

JCO7 Rec'd PCT/PTO 22 FEB 2002

SUBSTITUTE FORM PTO-1390

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

ATTORNEY'S DOCKET NUMBER  
06275-244001

U.S. APPLICATION NO. (If Known, see 37 CFR  
1.5) **10/069215**

INTERNATIONAL APPLICATION NO.  
PCT/GB00/03179

INTERNATIONAL FILING DATE  
August 18, 2000

PRIORITY DATE CLAIMED  
August 24, 1999

TITLE OF INVENTION  
SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

APPLICANT(S) FOR DO/EO/US  
Stephen Thom, Andrew Baxter, Nicholas Kindon, Thomas McNally, Brian Springthorpe, Matthew Perry, David Harden, Richard Evans and David Marriott

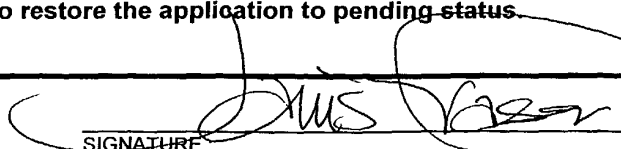
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1.  This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2.  This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3.  This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4.  The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5.  A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a.  is attached hereto (required only if not communicated by the International Bureau).
  - b.  has been communicated by the International Bureau.
  - c.  is not required, as the application was filed in the United States Receiving Office (RO/US).
6.  An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7.  Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a.  are attached hereto (required only if not communicated by the International Bureau).
  - b.  have been communicated by the International Bureau.
  - c.  have not been made; however, the time limit for making such amendments has NOT expired.
  - d.  have not been made and will not be made.
8.  An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9.  An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10.  An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11 to 16 below concern other documents or information included:**

11.  An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12.  An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13.  A **FIRST** preliminary amendment.  
 A **SECOND** or **SUBSEQUENT** preliminary amendment.
14.  A substitute specification.
15.  A change of power of attorney and/or address letter.
16.  Other items or information:

|   |                      |   |
|---|----------------------|---|
| CERTIFICATE OF MAILING BY EXPRESS MAIL  |                      | Express Mail Label No. <b>EL228026051US</b> |
| I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, DC 20231 |                      |   |
| February 22, 2002   | <i>Henry Jenkins</i> | <i>Henry Jenkins</i>                        |
| Date of Deposit   | Signature            | Typed Name of Person Signing                |

|   |              |   |  |
|---|--------------|---|--|
| U.S. APPLICATION NO. (IF KNOWN)<br><b>10/069215</b>   |              | INTERNATIONAL APPLICATION NO.<br>PCT/GB00/03179   | ATTORNEY'S DOCKET NUMBER<br>06275-244001 |
| 17. <input checked="" type="checkbox"/> The following fees are submitted:<br><b>Basic National Fee ( 37 CFR 1.492(a)(1)- (5) ):</b><br>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... <b>\$1040</b><br><br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$890</b><br><br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$740</b><br><br>International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$710</b><br><br>International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$100</b><br><br><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b> |              | <b>CALCULATIONS PTO USE ONLY</b>  |  |
|   |              | <b>\$890.00</b>   |  |
| Surcharge of <b>\$130</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).   |              | <b>\$0.00</b>   |  |
| Claims  | Number Filed | Number Extra  | Rate                                     |
| Total Claims  | 11 - 20 =    | 0   | x <b>\$18</b>                            |
| Independent Claims  | 3 - 3 =      | 0   | x <b>\$84</b>                            |
| MULTIPLE DEPENDENT CLAIMS(S) (if applicable)  |              |   | + <b>\$280</b>                           |
| <b>TOTAL OF ABOVE CALCULATIONS =</b>  |              | <b>\$890.00</b>   |  |
| <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.  |              | <b>\$0.00</b>   |  |
| <b>SUBTOTAL =</b>   |              | <b>\$890.00</b>   |  |
| Processing fee of <b>\$130</b> for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))   |              | <b>\$0.00</b>   |  |
| <b>TOTAL NATIONAL FEE =</b>   |              | <b>\$890.00</b>   |  |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +   |              | <b>\$0.00</b>   |  |
| <b>TOTAL FEES ENCLOSED =</b>  |              | <b>\$890.00</b>   |  |
|   |              | <b>Amount to be refunded:</b>   | <b>\$</b>                                |
|   |              | <b>Charged:</b>   | <b>\$</b>                                |
| <p>a. <input checked="" type="checkbox"/> A check in the amount of \$890.00 to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. 06-1050 in the amount of \$0.00 to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.</p> <p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.</b></p>   |              |   |  |
| SEND ALL CORRESPONDENCE TO:   |              |   |  |
| Janis K. Fraser, Ph.D., J.D.<br>FISH & RICHARDSON P.C.<br>225 Franklin Street<br>Boston, Massachusetts 02110-2804<br>(617) 542-5070 phone<br>(617) 542-8906 facsimile   |              | <br>SIGNATURE |  |
|   |              | NAME<br><b>Janis K. Fraser, Ph.D., J.D.</b>   |  |
|   |              | REGISTRATION NUMBER<br><b>34,819</b>  |  |

JC19 Rec'd PCT/PTO 22 FEB 2007

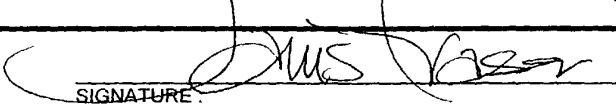
|   |              |   |   |
|---|--------------|---|---|
| APPLICATION NO. (IF KNOWN)<br><b>10/069215</b>  |              | INTERNATIONAL APPLICATION NO.<br>PCT/GB00/03179 | ATTORNEY'S DOCKET NUMBER<br>06275-244001                                  |
| <input checked="" type="checkbox"/> The following fees are submitted:<br><b>Basic National Fee ( 37 CFR 1.492(a)(1)- (5) ):</b><br>Other international preliminary examination fee (37 CFR 1.482)<br>International search fee (37 CFR 1.445(a)(2)) paid to USPTO<br>International Search Report not prepared by the EPO or JPO..... <b>\$1040</b><br><br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$890</b><br><br>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$740</b><br><br>International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$710</b><br><br>International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$100</b><br><br><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b> |              |   | CALCULATIONS PTO USE ONLY<br><br><br><br><br><br><br><br><br><br>\$890.00 |
| surcharge of <b>\$130</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).   |              |   | \$0.00  |
| Claims  | Number Filed | Number Extra                                    | Rate  |
| Total Claims  | 11 - 20 =    | 0   | x <b>\$18</b>   |
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| MULTIPLE DEPENDENT CLAIMS(S) (if applicable)  |              |   | + <b>\$280</b>  |
| <b>TOTAL OF ABOVE CALCULATIONS =</b>  |              |   | \$890.00  |
| Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.   |              |   | \$0.00  |
| <b>SUBTOTAL =</b>   |              |   | \$890.00  |
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| <b>TOTAL NATIONAL FEE =</b>   |              |   | \$890.00  |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +   |              |   | \$0.00  |
| <b>TOTAL FEES ENCLOSED =</b>  |              |   | \$890.00  |
|   |              |   | Amount to be refunded: \$   |
|   |              |   | Charged: \$   |

- A check in the amount of \$890.00 to cover the above fees is enclosed.
- Please charge my Deposit Account No. 06-1050 in the amount of \$0.00 to cover the above fees. A duplicate copy of this sheet is enclosed.
- The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

Janis K. Fraser, Ph.D., J.D.  
 H & RICHARDSON P.C.  
 5 Franklin Street  
 Boston, Massachusetts 02110-2804  
 7) 542-5070 phone  
 7) 542-8906 facsimile

SIGNATURE: 

NAME: Janis K. Fraser, Ph.D., J.D.

REGISTRATION NUMBER: 34,819

107069215

Attorney's Docket No.: 06275-244001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Stephen Thom et al.                      Art Unit : Unknown  
Serial No. :    Examiner : Unknown  
Filed : Herewith  
Title : SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF  
CHEMOKINE RECEPTOR ACTIVITY

**Box PCT**

Commissioner for Patents  
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the claims:

Amend claims 3, 4, and 7-9 as follows:

-- 3. (Amended) A compound according to claim 1, wherein T represents a group NH, C(O)NH or NHC(O)NH.

4. (Amended) A compound according to claim 1, wherein X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are all CH<sub>2</sub>.

7. (Amended) A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

CERTIFICATE OF MAILING BY EXPRESS MAIL

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February 22, 2002  
Date of Deposit

Leroy Jenkins  
Signature

Leroy Jenkins  
Typed or Printed Name of Person Signing Certificate

Applicant : Stephen Thom et al.  
Serial No. :  
Filed : Herewith  
Page : 2

8. (Amended) A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. (Amended) A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 for use in therapy. --



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Page : 3

Attorney's Docket No.: 06275-244001

REMARKS

Claims 1 to 11 are pending in this application, claims 3, 4 and 7-9 having been amended to delete multiple dependency. No new matter has been added.

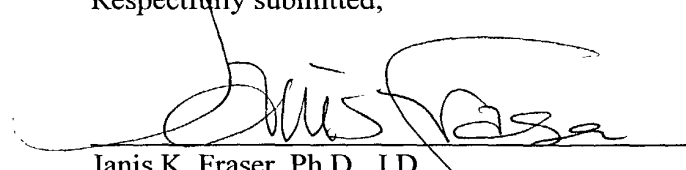
Attached is a marked-up version of the changes being made by the current amendment.

Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date:

Feb. 22, 2002

  
Janis K. Fraser, Ph.D., J.D.  
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Boston, Massachusetts 02110-2804  
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20387821 doc

Applicant : Stephen Thom et al.  
Serial No. :  
Filed : Herewith  
Page : 4

Attorney's Docket No.: 06275-244001

**Version with markings to show changes made**

In the claims:

Claim 3, 4 and 7-9 have been amended as follows:

-- 3. (Amended) A compound according to claim 1 [or claim 2], wherein T represents a group NH, C(O)NH or NHC(O)NH.

4. (Amended) A compound according to [any one of claims 1 to 3] claim 1, wherein X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are all CH<sub>2</sub>.

7. (Amended) A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in [any one of claims 1 to 4] claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. (Amended) A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, [as claimed in any one of claims 1 to 4] with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. (Amended) A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in [any one of claims 1 to 4] claim 1 for use in therapy. --

WO 01/14333

PCT/GB00/03179

## SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

The present invention relates to substituted piperidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

5

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved  
10 four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

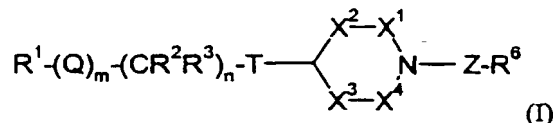
15 The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and  
20 MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 $\alpha$  and 1 $\beta$  (MIP-1 $\alpha$  and MIP-1 $\beta$ ).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2,  
25 CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

30 The present invention provides a compound of formula (I):





wherein

Z is  $CR^4R^5$ , C(O) or  $CR^4R^5-Z^1$ ;

$Z^1$  is  $C_{1-4}$  alkylene (such as  $CH_2$ ),  $C_{2-4}$  alkenylene (such as  $CH=CH$ ) or  $C(O)NH$ ;

5  $R^1$  represents a  $C_1-C_{12}$  alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl,  $C_1-C_6$  alkoxy (such as methoxy or ethoxy),  $C_1-C_6$  alkylthio (such as methylthio),  $C_3-7$  cycloalkyl (such as cyclopropyl),  $C_1-C_6$  alkoxy-carbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano,  $C_1-C_6$  alkyl,  $C_1-C_6$  haloalkyl (such as  $CF_3$ ), phenyl( $C_1-C_6$  alkyl) (such as benzyl),  $C_1-C_6$  alkoxy,  $C_1-C_6$  haloalkoxy,  $S(O)_2(C_1-C_6$  alkyl),  $C(O)NH_2$ ,  
10 carboxy or  $C_1-C_6$  alkoxy-carbonyl); or

$R^1$  represents  $C_2-C_6$  alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano,  $C_1-C_6$  alkyl,  $C_1-C_6$  haloalkyl, phenyl( $C_1-C_6$  alkyl),  $C_1-C_6$  alkoxy,  $C_1-C_6$  haloalkoxy,  $S(O)_2(C_1-C_6$  alkyl),  $C(O)NH_2$ , carboxy or  $C_1-C_6$  alkoxy-carbonyl); or  
15

$R^1$  represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents  
20 independently selected from: halogen, cyano, nitro, oxo, hydroxyl,  $C_1-C_8$  alkyl,  $C_1-C_6$  hydroxyalkyl,  $C_1-C_6$  haloalkyl,  $C_{1-6}$  alkoxy( $C_1-C_6$  alkyl),  $C_3-C_7$  cycloalkyl( $C_1-C_6$  alkyl),  $C_1-C_6$  alkylthio( $C_1-C_6$  alkyl),  $C_1-C_6$  alkylcarbonyloxy( $C_1-C_6$  alkyl),  $C_1-C_6$  alkyl $S(O)_2(C_1-C_6$  alkyl), aryl( $C_1-C_6$  alkyl), heterocyclyl( $C_1-C_6$  alkyl), aryl $S(O)_2(C_1-C_6$  alkyl), heterocyclyl $S(O)_2(C_1-C_6$  alkyl), aryl( $C_1-C_6$  alkyl) $S(O)_2$ , heterocyclyl( $C_1-C_6$  alkyl) $S(O)_2$ ,  
25  $C_2-C_6$  alkenyl,  $C_1-C_6$  alkoxy, carboxy-substituted  $C_1-C_6$  alkoxy,  $C_1-C_6$  haloalkoxy,  $C_1-C_6$  hydroxyalkoxy,  $C_1-C_6$  alkylcarboxy-substituted  $C_1-C_6$  alkoxy, aryloxy, heterocyclyloxy,  $C_1-C_6$  alkylthio,  $C_3-C_7$  cycloalkyl( $C_1-C_6$  alkylthio),  $C_3-C_6$  alkynylthio,  $C_1-C_6$  alkylcarbonylamino,  $C_1-C_6$  haloalkylcarbonylamino,  $SO_3H$ ,  $-NR^7R^8$ ,  $-C(O)NR^{23}R^{24}$ ,  $S(O)_2NR^{18}R^{19}$ ,  $S(O)_2R^{20}$ ,  $R^{25}C(O)$ , carboxyl,  $C_1-C_6$  alkoxy-carbonyl, aryl and heterocyclyl;  
30 wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or

more of halogen, oxo, hydroxy, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl;

m is 0 or 1;

5 Q represents an oxygen or sulphur atom or a group NR<sup>9</sup>, C(O), C(O)NR<sup>9</sup>, NR<sup>9</sup>C(O) or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R<sup>2</sup> and R<sup>3</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group, or (CR<sup>2</sup>R<sup>3</sup>)<sub>n</sub> represents C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub> alkyl;

10 T represents a group NR<sup>10</sup>, C(O)NR<sup>10</sup>, NR<sup>11</sup>C(O)NR<sup>10</sup> or C(O)NR<sup>10</sup>NR<sup>11</sup>;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are, independently, CH<sub>2</sub>, CHR<sup>12</sup> {wherein each R<sup>12</sup> is, independently, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)} or C=O; or, when they are CHR<sup>12</sup>, the R<sup>12</sup> groups of X<sup>1</sup> and X<sup>3</sup> or X<sup>4</sup>, or X<sup>2</sup> and X<sup>3</sup> or X<sup>4</sup> join to form a two or three atom chain which is CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>OCH<sub>2</sub> or CH<sub>2</sub>SCH<sub>2</sub>; provided always that at least two

15 of X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are CH<sub>2</sub>;

R<sup>4</sup> and R<sup>5</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

R<sup>6</sup> is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1-6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub>

20 alkylcarbonyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl),

heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl), arylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heterocyclioxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-

25 C<sub>6</sub> alkylthio), C<sub>3</sub>-C<sub>6</sub> alkynylthio, C<sub>1</sub>-C<sub>6</sub> alkylcarbonylamino, C<sub>1</sub>-C<sub>6</sub>

haloalkylcarbonylamino, SO<sub>3</sub>H, -NR<sup>16</sup>R<sup>17</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, S(O)<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, S(O)<sub>2</sub>R<sup>15</sup>,

R<sup>26</sup>C(O), carboxyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy,

30 S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl;

$R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}$  and  $R^{24}$  are, independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl); and,

$R^{15}$  and  $R^{20}$  are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by phenyl;

$R^{25}$  and  $R^{26}$  are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is C(O)NR<sup>10</sup> and R<sup>1</sup> is optionally substituted phenyl then n is not 0.

Certain compounds of formula (I) are capable of existing in isomeric forms (for example as tautomers, enantiomers, geometric isomers or diastereomers). The present invention encompasses all such isomers and mixtures thereof in all proportions.

Hydroxyalkyl is, for example, 2-hydroxyethyl. Haloalkyl is, for example, CF<sub>3</sub>. Alkoxy is, for example, methoxy or ethoxy. Alkoxy(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, methoxymethyl or ethoxyethyl. Cycloalkyl is, for example, cyclopropyl or cyclohexyl. Cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, cyclopropylmethyl. Alkylthio is, for example, methylthio or ethylthio. Alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, methylthiomethyl. Alkylcarbonyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, CH<sub>3</sub>C(O)OCH<sub>2</sub>. S(O)<sub>2</sub>(alkyl) is, for example, CH<sub>3</sub>S(O)<sub>2</sub>. AlkylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, CH<sub>3</sub>S(O)<sub>2</sub>CH<sub>2</sub>. Aryl(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, benzyl, 2-phenyleth-1-yl or 1-phenyleth-1-yl. Heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, heterocyclylmethyl. ArylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, phenylS(O)<sub>2</sub>CH<sub>2</sub>. HeterocyclylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl) is, for example, heterocyclylS(O)<sub>2</sub>CH<sub>2</sub>. Aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub> is, for example, benzylS(O)<sub>2</sub>. Heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub> is, for example, heterocyclylCH<sub>2</sub>S(O)<sub>2</sub>. Alkenyl is, for example, vinyl or allyl. Carboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy is, for example, HOC(O)CH<sub>2</sub>CH<sub>2</sub>O. Haloalkoxy is, for example, OCF<sub>3</sub>. Hydroxyalkoxy is, for example, HOCH<sub>2</sub>CH<sub>2</sub>O. Alkylcarboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy is, for example, CH<sub>3</sub>OC(O)CH<sub>2</sub>CH<sub>2</sub>O. Aryloxy is, for example, phenoxy.

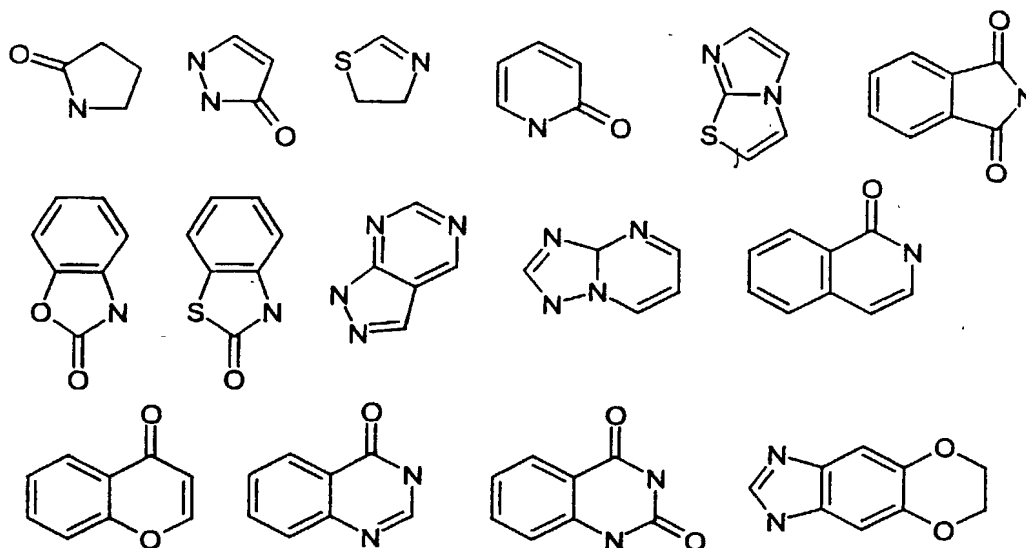
Heterocycloxy is, for example, pyridinyloxy or pyrimidinyloxy. C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkylthio) is, for example, cyclopropylCH<sub>2</sub>S. Alkynylthio is, for example, propargylthio. Alkylcarbonylamino is, for example, acylamino. Haloalkylcarbonylamino is, for example, ClCH<sub>2</sub>C(O)NH. Alkoxy carbonyl is, for example, CH<sub>3</sub>OC(O).

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Aryl is a carbocyclic aromatic ring optionally fused to one or more carbocyclic rings. Aryl is, for example, phenyl, naphthyl or indanyl.

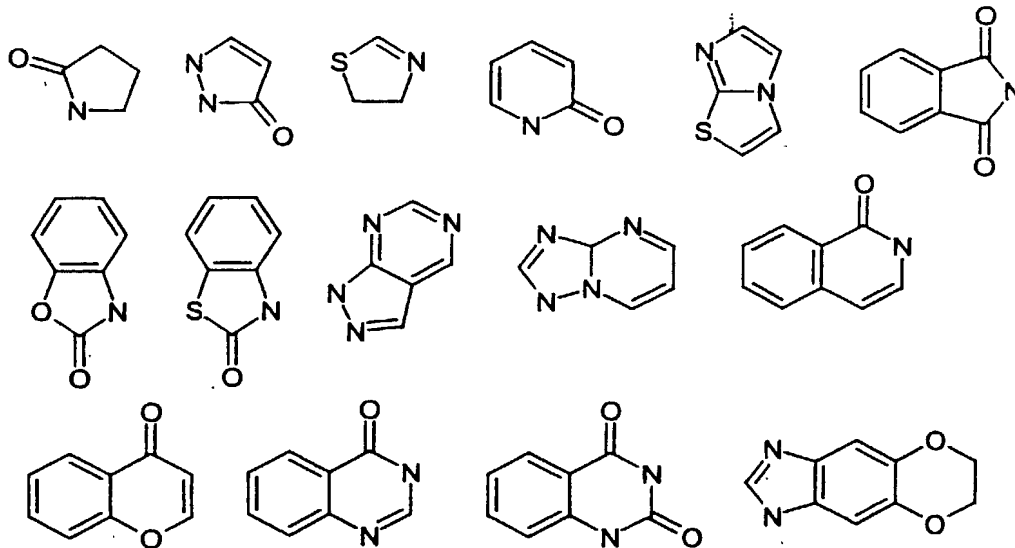
Heterocyclyl is an aromatic or non-aromatic ring system preferably comprising up to 6  
10 (preferably up to 4) heteroatoms selected from the group comprising nitrogen, oxygen and sulphur, and preferably comprising one, two or three 5- or 6-membered rings.

Heterocyclyl is, for example, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,  
15 pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as  
20 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxaliny, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl  
25 (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:

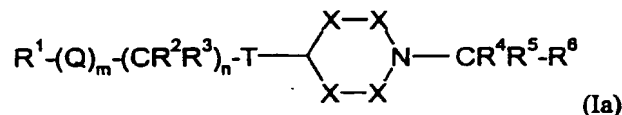


The group  $R^1$  may represent an optionally substituted 3- to 14-membered (especially 5- to 10-membered) saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of  $R^1$  ring systems, which can be monocyclic or polycyclic, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-

d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazoliny or dibenzothiophenyl; or a ring as shown below:



- 5 In one aspect the present invention provides a compound of formula (Ia):



wherein

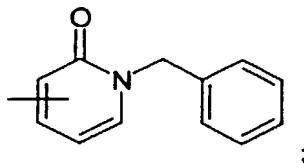
$R^1$  represents a  $C_1$ - $C_{12}$  alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio and

- 10  $C_1$ - $C_6$  alkoxycarbonyl, or

$R^1$  represents a 3- to 10-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents

15 independently selected from halogen, cyano, nitro, hydroxyl, carboxyl,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  hydroxyalkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkoxy, carboxy-substituted  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio,  $C_1$ - $C_6$  alkylthiomethyl,  $C_1$ - $C_6$  alkylcarbonylamino,  $-NR^7R^8$ ,  $-C(O)NR^7R^8$ ,  $C_1$ - $C_6$

alkylcarbonyloxymethyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl piperazinyl, furyl, phenyl, pyridinyl, pyrazinyl, halophenyl, thienyl, thienylmethyl, C<sub>1</sub>-C<sub>6</sub> alkylbenzyl and



m is 0 or 1;

- 5 Q represents an oxygen or sulphur atom or a group NR<sup>9</sup>, C(O), C(O)NR<sup>9</sup> or NR<sup>9</sup>C(O);  
 n is 0, 1, 2, 3 or 4, provided that when n is 0, then m is 0;  
 each R<sup>2</sup> and R<sup>3</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;  
 T represents a group NR<sup>10</sup>, C(O)NR<sup>10</sup> or NR<sup>11</sup>C(O)NR<sup>10</sup>;  
 each X independently represents a group CH<sub>2</sub>, CHR<sup>12</sup> or C=O, provided that at least two  
 10 groups X simultaneously represent CH<sub>2</sub>;  
 R<sup>4</sup> and R<sup>5</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;  
 R<sup>6</sup> represents a phenyl group optionally substituted by one or more substituents  
 independently selected from halogen, amino (-NH<sub>2</sub>), nitro, cyano, sulphonyl (-SO<sub>3</sub>H),  
 sulphonamido (-SO<sub>2</sub>NH<sub>2</sub>), C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy and C<sub>1</sub>-C<sub>6</sub> alkylsulphonyl;  
 15 R<sup>7</sup> and R<sup>8</sup> each independently represent a hydrogen atom or a group selected from  
 C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl and C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by phenyl; R<sup>9</sup>,  
 R<sup>10</sup> and R<sup>11</sup> each independently represent a hydrogen atom, or a C<sub>1</sub>-C<sub>4</sub> alkyl or  
 cyclopropylmethyl group; and  
 each R<sup>12</sup> independently represents a C<sub>1</sub>-C<sub>4</sub> alkyl or cyclopropylmethyl group;  
 20 or a pharmaceutically acceptable salt or solvate thereof.

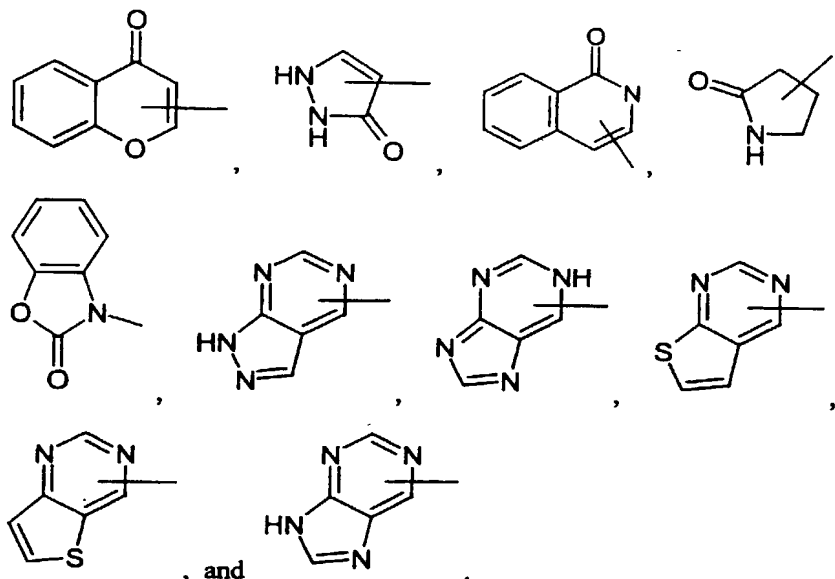
In the context of the present specification, unless otherwise indicated an alkyl substituent  
 or an alkyl moiety in a substituent group may be linear or branched. Examples of alkyl  
 groups/moieties containing up to twelve carbon atoms include methyl, ethyl, n-propyl, iso-  
 25 propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl,  
 n-undecyl and n-dodecyl groups. A C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl group will comprise at least one  
 hydroxyl group (e.g. one, two or three hydroxyl groups) which may be attached to an  
 internal or terminal carbon atom of the alkyl chain. Similarly, a carboxy-substituted  
 C<sub>1</sub>-C<sub>6</sub> alkoxy group will comprise at least one carboxyl group (e.g. one, two or three

carboxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. A C<sub>1</sub>-C<sub>6</sub> haloalkyl or C<sub>1</sub>-C<sub>6</sub> haloalkoxy group will comprise at least one halogen atom (e.g. one, two, three or four halogen atoms independently selected from fluorine, chlorine, bromine and iodine) which may be attached to an internal or terminal carbon atom of the alkyl chain. A halophenyl group will comprise from 1 to 5 halogen atoms independently selected from fluorine, chlorine, bromine and iodine. A C<sub>1</sub>-C<sub>6</sub> alkylbenzyl group will comprise at least one C<sub>1</sub>-C<sub>6</sub> alkyl group (e.g. one, two or three C<sub>1</sub>-C<sub>6</sub> alkyl groups) attached to the phenyl ring of the benzyl moiety. If there is more than one C<sub>1</sub>-C<sub>6</sub> alkyl group attached to the phenyl ring, the groups may be the same or different. In a C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl piperazinyl substituent group, the piperazinyl moiety is attached through a nitrogen atom to the carbonyl moiety. When T represents C(O)NR<sup>9</sup>, it should be understood that the nitrogen atom is attached directly to the six-membered heterocyclic ring in formula (I).

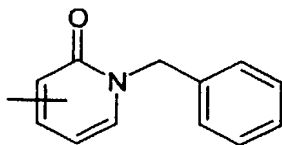
The group R<sup>1</sup> may represent a C<sub>1</sub>-C<sub>12</sub>, preferably C<sub>1</sub>-C<sub>10</sub>, more preferably C<sub>1</sub>-C<sub>6</sub>, alkyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from cyano, hydroxyl, C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkoxy, C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkylthio and C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, preferably C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl.

The group R<sup>1</sup> may alternatively represent an optionally substituted 3- to 10-membered saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used which can be monocyclic or polycyclic include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyrazolyl, furyl, thienyl, imidazolyl, quinolinyl (e.g. 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), pyridinyl (e.g. 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), 1,3-benzodioxolyl, thiazolyl, benzimidazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl), triazolyl (such as 1,2,3-triazolyl or 1,2,4-triazolyl), benzothiazolyl, pyrimidinyl (e.g. 2-pyrimidinyl or 4-pyrimidinyl), benzothienyl,





- 5 In a further aspect of the invention the ring system of  $R^1$  may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine); cyano; nitro; hydroxyl; carboxyl;  $C_1-C_6$ , preferably  $C_1-C_4$ , alkyl (especially methyl or ethyl);  $C_1-C_6$ , preferably  $C_1-C_4$ , hydroxyalkyl;  $C_1-C_6$ , preferably  $C_1-C_4$ , haloalkyl (e.g. trifluoromethyl);  $C_1-C_6$ , preferably
- 10  $C_1-C_4$ , alkoxy (especially methoxy, ethoxy, n-propoxy or isopropoxy); carboxy-substituted  $C_1-C_6$ , preferably  $C_1-C_4$ , alkoxy;  $C_1-C_6$ , preferably  $C_1-C_4$ , alkylthio (especially methylthio, ethylthio, n-propylthio and tert-butylthio);  $C_1-C_6$ , preferably  $C_1-C_4$ , alkylthiomethyl (particularly methylthiomethyl);  $C_1-C_6$ , preferably  $C_1-C_4$ , alkylcarbonylamino (especially methylcarbonylamino);  $-NR^7R^8$ ;  $-C(O)NR^7R^8$ ;  $C_1-C_6$ , preferably  $C_1-C_4$ ,
- 15 alkylcarbonyloxymethyl (particularly methylcarbonyloxymethyl);  $C_1-C_6$ , preferably  $C_1-C_4$ , alkoxycarbonyl (especially methoxycarbonyl or ethoxycarbonyl);  $C_1-C_6$ , preferably  $C_1-C_4$ , alkoxycarbonylpiperazinyl; furyl; phenyl; pyridinyl; pyrazinyl; halophenyl (especially chlorophenyl); thienyl; thienylmethyl;  $C_1-C_6$ , preferably  $C_1-C_4$ , alkylbenzyl (particularly methylbenzyl); and



In a further aspect  $R^1$  is an aromatic 5-membered heterocyclyl having 2, 3 or 4 ring nitrogen atoms (for example 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole or tetrazole) substituted by one heteroaromatic ring (such as pyridine or pyrazole) which is itself optionally substituted by halogen or  $C_1$ - $C_4$  alkyl; or  $R^1$  is halophenyl (for example phenyl optionally substituted (such as in the 4-position) by fluoro or chloro; such as 4-chlorophenyl or 4-fluorophenyl).

In a further aspect of the invention Q is oxygen or m is 0. In another aspect of the invention Q represents a sulphur atom or a group NH, C(O) or NHC(O).

In yet another aspect of the invention n is 1 or 2.

In a further aspect of the invention T represents a group NH, C(O)NH or NHC(O)NH. In another aspect of the invention T represents a NH or C(O)NH group. In a further aspect T is C(O)NH.

In one aspect  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are all  $CH_2$  or  $CHR^{12}$ , wherein the  $R^{12}$  groups of  $X^1$  and  $X^3$  or  $X^4$ , or,  $X^2$  and  $X^3$  or  $X^4$  join to form  $CH_2CH_2$ ; provided always that at least two of  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are  $CH_2$ . In a still further aspect  $X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  are all  $CH_2$ . Preferably, all four groups X represent  $CH_2$ .

It is preferred that each  $R^2$  and  $R^3$  independently represents a hydrogen atom or a methyl group, especially a hydrogen atom.

In one aspect  $R^4$  and  $R^5$  are hydrogen or  $C_1$ - $C_4$  alkyl. In another aspect  $R^4$  and  $R^5$  preferably each represent a hydrogen atom.

In another aspect of the invention R<sup>6</sup> represents a phenyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkyl, C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, haloalkoxy, methylenedioxy and C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkylsulphonyl.

In another aspect of the invention R<sup>6</sup> represents a phenyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkyl, C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, haloalkoxy and C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkylsulphonyl.

In a further aspect R<sup>6</sup> is phenyl optionally substituted by halogen or methylenedioxy. In a still further aspect R<sup>6</sup> is most preferably a phenyl group substituted by halogen. Examples of R<sup>6</sup> include 3-chlorophenyl, 4-chlorophenyl or, especially, 3,4-dichlorophenyl.

R<sup>7</sup> and R<sup>8</sup> each independently represent a hydrogen atom or a group selected from C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) and C<sub>1</sub>-C<sub>6</sub>, preferably C<sub>1</sub>-C<sub>4</sub>, alkyl optionally substituted by phenyl (e.g. one or two phenyl groups).

Most preferably, R<sup>7</sup> and R<sup>8</sup> each independently represent a hydrogen atom, or a group selected from C<sub>2</sub> hydroxyalkyl, cyclopropyl and C<sub>1</sub>-C<sub>2</sub> alkyl optionally substituted by phenyl.

Compounds of the invention include all the Examples below, some of which are:

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(4-methylbenzyl)amine,  
N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidiny]amino}methyl)phenyl]acetamide,  
3-({[1-(3,4-Dichlorobenzyl)-4-piperidiny]amino}methyl)phenol,  
N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-[(5-methyl-2-furyl)methyl]amine,

- N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine,  
N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine,  
N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
5 N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine,  
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol,  
10 4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,  
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one,  
N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-  
piperidinamine,  
N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
15 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{{[1-(4-methylbenzyl)-1H-pyrazol-5-  
yl]methyl}amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine,  
N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine,  
20 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine,  
[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate,  
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-  
dihydro-3H-pyrazol-3-one,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine,  
25 5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,  
N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine,  
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid,  
N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
30 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine,

- N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine,  
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic  
acid,  
N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic  
acid,  
N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine,  
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-  
one,  
10 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-  
yl)methyl]amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine,  
15 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine,  
Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-  
yl]butanamide,  
20 2-{{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-  
N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide,  
25 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-  
isoquinoliny)butanamide,  
3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide,  
30 2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-  
piperidinyl]acetamide,

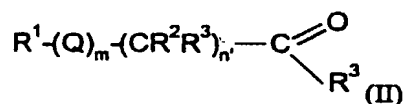
- N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide,  
2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-4-(3,4-dimethoxyphenyl)butanamide,  
5 5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]pentanamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-fluoro-2-methylbenzamide,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-(1-phenylethyl)phthalamide,  
2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide,  
4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-nitrobenzamide,  
10 2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-1-methylcyclopropanecarboxamide,  
*tert*-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidiny]amino} carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide,  
15 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-4-fluorobenzamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-methylbenzamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-methylbenzamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-4-(hydroxymethyl)benzamide,  
20 N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-(2-[(methylsulfanyl)methyl]-4-pyrimidinyl)-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-(2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl)-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine,  
25 2-({4-([1-(3,4-Dichlorobenzyl)-4-piperidiny]amino) ethyl}amino)-2-pyrimidinyl} amino)-1-ethanol,  
N<sup>4</sup>-(2-([1-(3,4-Dichlorobenzyl)-4-piperidiny]amino) ethyl)-6-methyl-2,4-pyrimidinediamine,  
30 N<sup>4</sup>-(2-([1-(3,4-Dichlorobenzyl)-4-piperidiny]amino) ethyl)-N<sup>2</sup>,6-dimethyl-2,4-pyrimidinediamine,

- 2-Chloro-N<sup>4</sup>-cyclopropyl-N<sup>6</sup>-(2-{{1-(3,4-dichlorobenzyl)-4-piperidinyl}amino} ethyl)-4,6-pyrimidinediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine,  
5 N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine,  
N<sup>2</sup>-(2-{{1-(3,4-Dichlorobenzyl)-4-piperidinyl}amino} ethyl)-N<sup>4</sup>,6-dimethyl-2,4-pyrimidinediamine,  
10 N<sup>4</sup>-Cyclopropyl-N<sup>2</sup>-(2-{{1-(3,4-dichlorobenzyl)-4-piperidinyl}amino} ethyl)-2,4-pyrimidinediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine,  
15 N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine,  
20 N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(1H-purin-6-yl)-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine,  
N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine,  
25 N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{{5-(trifluoromethyl)-2-pyridinyl}sulfanyl}acetamide,  
30 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide,  
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide,

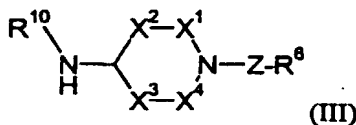
- 2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(phenylsulfanyl)acetamide,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(4-fluorophenyl)acetamide,  
 5 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-1H-benzimidazol-2-amine,  
 10 2-[[1-(3,4-Dichlorobenzyl)-4-piperidiny]amino]-N-(3-methoxyphenyl)acetamide, dihydrochloride salt,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N'-(3,4-dichlorophenyl)urea,  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N'-(3-methoxyphenyl)urea, and  
 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(4-methoxybenzyl)amine, dihydrochloride  
 15 salt.

The present invention further provides a process for the preparation of a compound of formula (I) or (Ia) which comprises:

- (a) when n is at least 1, the  $CR^2R^3$  group attached directly to T is  $CHR^3$  and T is  $NR^{10}$ ,  
 20 reacting a compound of formula



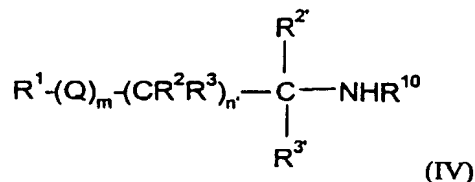
wherein n' is 0 or an integer from 1 to 3 and  $R^1$ ,  $R^2$ ,  $R^3$ , m and Q are as defined above, with a compound of formula



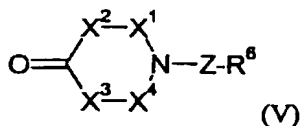
- 25 or a salt thereof, wherein  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , Z,  $R^6$  and  $R^{10}$  are as defined above, in the presence of a reducing agent; or



(b) when n is at least 1, the CR<sup>2</sup>R<sup>3</sup> group attached directly to T is C(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and T is NR<sup>10</sup>, reacting a compound of formula



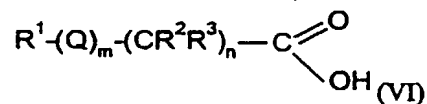
wherein n' is 0 or an integer from 1 to 3, R<sup>2</sup> and R<sup>3</sup> each independently represent a C<sub>1</sub>-C<sub>4</sub> alkyl group, and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>10</sup>, m and Q are as defined above, with a compound of formula



wherein X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, Z and R<sup>6</sup> are as defined above, in the presence of a reducing agent; or

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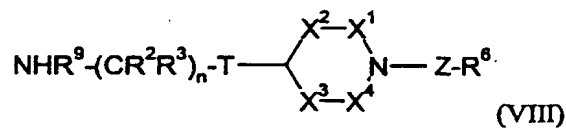
(c) when T is C(O)NR<sup>10</sup>, reacting a compound of formula



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, Q, m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above; or

15

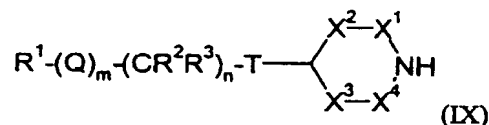
(d) when m is 1 and Q is NR<sup>9</sup>, reacting a compound of formula (VII), R<sup>1</sup>-L<sup>1</sup>, wherein L<sup>1</sup> represents a leaving group (e.g. a halogen atom) and R<sup>1</sup> is as defined above, with a compound of formula



or a salt thereof, wherein n, T, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, Z, R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and R<sup>9</sup> are as defined above; or

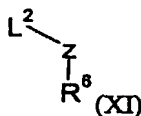
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(e) when at least one of  $R^4$  and  $R^5$  represents a hydrogen atom, reacting a compound of formula



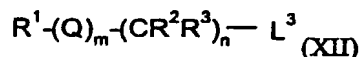
or a salt thereof, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $Q$ ,  $m$ ,  $n$ ,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$  and  $T$  are as defined above, with a compound of general formula (X),  $R^6-C(O)-R^{20}$ , wherein  $R^{20}$  represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl group and  $R^6$  is as defined above, in the presence of a reducing agent; or

(f) reacting a compound of formula (IX) as defined in (e) above, with a compound of formula



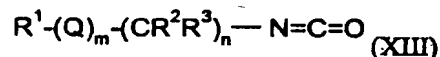
wherein  $L^2$  represents a leaving group (e.g. a halogen atom) and  $Z$  and  $R^6$  are as defined above; or

(g) when  $T$  is  $NR^{10}$ , reacting a compound of formula



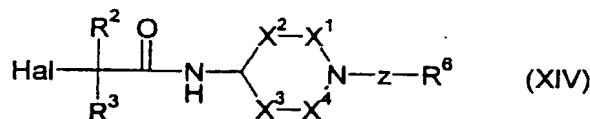
wherein  $L^3$  represents a leaving group (e.g. a halogen atom) and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $m$ ,  $n$  and  $Q$  are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above; or

(h) when  $T$  is  $NHC(O)NR^{10}$ , reacting a compound of formula



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $Q$ ,  $m$  and  $n$  are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above; or

(i) when  $T$  is  $C(O)NH$ ,  $Z$  is  $CH_2$ ,  $n$  is 1,  $R^2$  and  $R^3$  are hydrogen or  $C_1$ - $C_4$  alkyl and  $Q$  is oxygen or sulphur, reacting a compound of formula (XIV):



wherein Hal is a suitable halogen (such as bromo or chloro),  $\text{R}^2, \text{R}^3, \text{X}^1, \text{X}^2, \text{X}^3, \text{X}^4, \text{Z}$  and  $\text{R}^6$  are as defined above, with  $\text{R}^1\text{OH}$  or  $\text{R}^1\text{SH}$  in the presence of a suitable base (such as potassium carbonate or sodium or potassium hydroxide);

and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) or (Ia) obtained.

Compounds of formulae (II) to (XIV) are either commercially available, or are known in the literature or may be prepared using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) or (Ia) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

The compounds of formula (I) and (Ia) have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity. More particularly, the compounds have utility as modulators of the activity of chemokine receptors CCR1 and/or CCR3.

A further aspect of the invention involves the use of a compound of formula (I) or (Ia) in the treatment of conditions or diseases in which modulation of chemokine receptor activity is beneficial.

- 5 Thus, compounds of formula (I) or (Ia) may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS). Examples of these conditions include:
- 10 (1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis
- 15 medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;
- 20 (2) **(bone and joints)** rheumatoid arthritis, osteoarthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;
- (3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous
- 25 dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;
- (4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis,
- 30 mastocytosis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) (other tissues and systemic disease) multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fasciitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; and

(6) (allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

Thus, the present invention provides a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In another aspect the present invention provides the use of a compound of formula (I), wherein Z is  $CR^4R^5$ ,  $C(O)$  or  $CR^4R^5-Z^1$ ;  $Z^1$  is  $C_{1-4}$  alkylene,  $C_{2-4}$  alkenylene or  $C(O)NH$ ;  $R^1$

represents a C<sub>1</sub>-C<sub>12</sub> alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3-7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl); or R<sup>1</sup> represents C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl); or R<sup>1</sup> represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1-6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3-7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylcarbonyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl), arylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heterocycliloxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3-7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkylthio), C<sub>3-6</sub> alkynylthio, C<sub>1</sub>-C<sub>6</sub> alkylcarbonylamino, C<sub>1</sub>-C<sub>6</sub> haloalkylcarbonylamino, SO<sub>3</sub>H, -NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>23</sup>R<sup>24</sup>, S(O)<sub>2</sub>NR<sup>18</sup>R<sup>19</sup>, S(O)<sub>2</sub>R<sup>20</sup>, R<sup>25</sup>C(O), carboxyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl; m is 0 or 1; Q represents an oxygen or sulphur atom or a group NR<sup>9</sup>, C(O), C(O)NR<sup>9</sup>, NR<sup>9</sup>C(O) or CH=CH; n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0; each R<sup>2</sup> and R<sup>3</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group, or (CR<sup>2</sup>R<sup>3</sup>)<sub>n</sub> represents C<sub>3-7</sub> cycloalkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub> alkyl; T represents a group NR<sup>10</sup>, C(O)NR<sup>10</sup>, NR<sup>11</sup>C(O)NR<sup>10</sup> or C(O)NR<sup>10</sup>NR<sup>11</sup>; X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are, independently, CH<sub>2</sub>, CHR<sup>12</sup> {wherein each R<sup>12</sup> is, independently, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>3-7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)} or C=O; or, when they are

CHR<sup>12</sup>, the R<sup>12</sup> groups of X<sup>1</sup> and X<sup>3</sup> or X<sup>4</sup>, or, X<sup>2</sup> and X<sup>3</sup> or X<sup>4</sup> join to form a two or three atom chain which is CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>OCH<sub>2</sub> or CH<sub>2</sub>SCH<sub>2</sub>; provided always that at least two of X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are CH<sub>2</sub>; R<sup>4</sup> and R<sup>5</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group; R<sup>6</sup> is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1-6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylcarbonyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl), arylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heterocycliloxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkylthio), C<sub>3</sub>-C<sub>6</sub> alkynylthio, C<sub>1</sub>-C<sub>6</sub> alkylcarbonylamino, C<sub>1</sub>-C<sub>6</sub> haloalkylcarbonylamino, SO<sub>3</sub>H, -NR<sup>16</sup>R<sup>17</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, S(O)<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, S(O)<sub>2</sub>R<sup>15</sup>, R<sup>26</sup>C(O), carboxyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl; R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup> and R<sup>24</sup> are, independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl); R<sup>15</sup> and R<sup>20</sup> are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by phenyl; and, R<sup>25</sup> and R<sup>26</sup> are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, in the manufacture of a medicament for the modulation of a chemokine receptor (such as CCR1 or CCR3). In a further aspect such medicament is for the treatment of asthma.

The invention also provides a method of treating an inflammatory disease in a person suffering from, or at risk of, said disease, which comprises administering to the person a therapeutically effective amount of a compound of formula (I) or (Ia), or a

pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

A compound of formula (I) or (Ia) or a pharmaceutically acceptable salt, solvate or solvate of a salt, may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) or (Ia) compound, salt, solvate or solvate of salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders, aerosols or granules, or by parenteral administration in

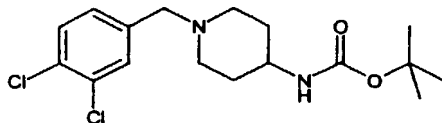


the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will be further explained by reference to the following illustrative examples.

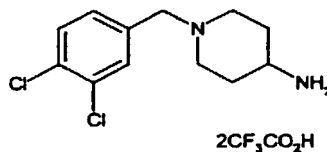
### Examples 1-47

#### (i) tert-Butyl 1-(3,4-dichlorobenzyl)-4-piperidinylcarbamate



Sodium triacetoxyborohydride (6g) was added to a stirred solution of 3,4-dichlorobenzaldehyde (4.2g) and 1,1-dimethylethyl-4-piperidinyl carbamate (4g) in dichloromethane (50ml). The mixture was stirred at room temperature for 4h then partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The organic layer was washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether to give a white solid (3.5g). Used directly.

#### (ii) 1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt



The product from step (i) (3.5g) was treated with trifluoroacetic acid (10ml) in dichloromethane (40ml). After 72h, the solution was evaporated, the residue triturated with ether and the solid (4.3g) collected.

MS: APCI(+ve) 259/61 (M+1)

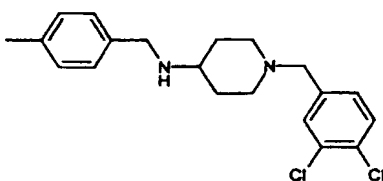
#### (iii) Examples 1-47

The product from step (ii) (2mg), the appropriate aldehyde (2 equivalents), sodium triacetoxyborohydride (3 equivalents) and diisopropylethylamine (2 equivalents) in

acetonitrile (0.08ml) and 1-methyl-2-pyrrolidinone (0.12ml) was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

5 **Example 1**

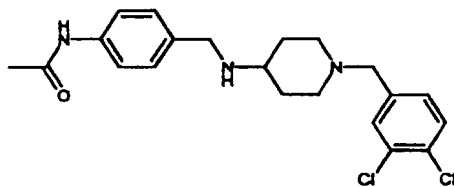
**N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(4-methylbenzyl)amine**



MS: APCI(+ve) 363 (M+1)

10 **Example 2**

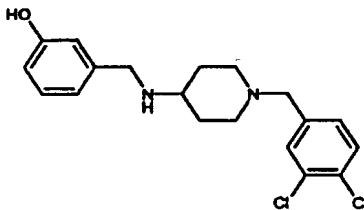
**N-[4-({1-(3,4-Dichlorobenzyl)-4-piperidiny]amino}methyl)phenyl]acetamide**



MS: APCI(+ve) 406 (M+1)

15 **Example 3**

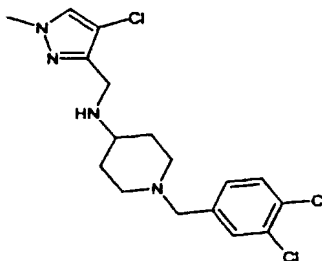
**3-({1-(3,4-Dichlorobenzyl)-4-piperidiny]amino}methyl)phenol**



MS: APCI(+ve) 365 (M+1)

20 **Example 4**

**N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine**

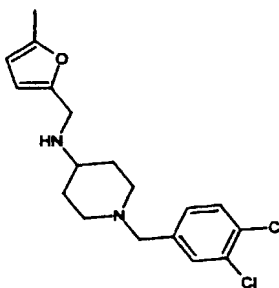


MS: APCI(+ve) 389 (M+1)

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**Example 5**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine**

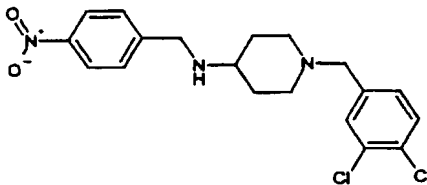


MS: APCI(+ve) 353 (M+1)

10

**Example 6**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine**



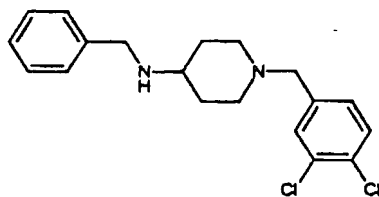
MS: APCI(+ve) 394 (M+1)

15

**Example 7**

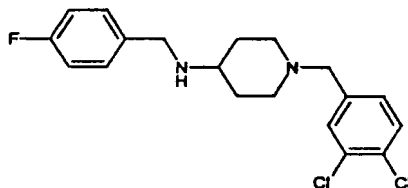
**N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine**

29

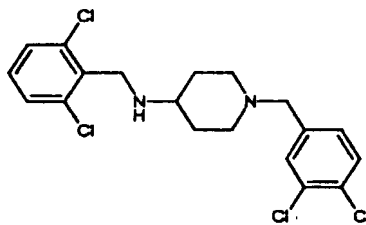


MS: APCI(+ve) 349 (M+1)

v

**Example 8**5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine**

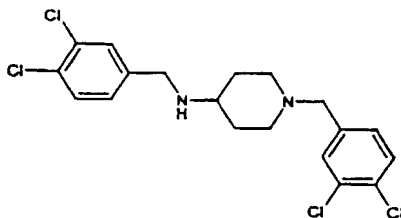
MS: APCI(+ve) 367 (M+1)

**Example 9**10 **N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine**

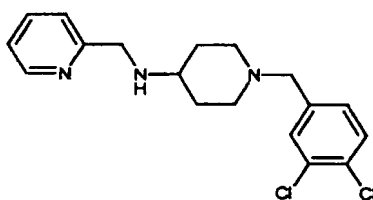
MS: APCI(+ve) 419 (M+1)

**Example 10**15 **N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine**

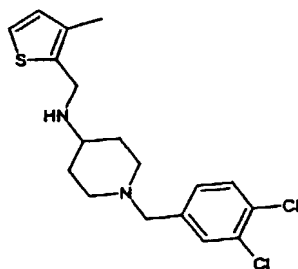
30



MS: APCI(+ve) 419 (M+1)

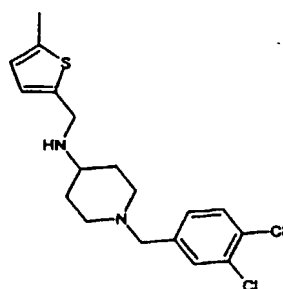
5 **Example 11****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine**

MS: APCI(+ve) 350 (M+1)

10 **Example 12****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine**

MS: APCI(+ve) 369 (M+1)

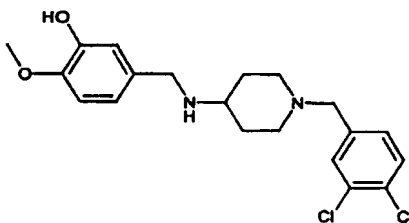
15 **Example 13****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine**



MS: APCI(+ve) 369 (M+1)

**Example 14**

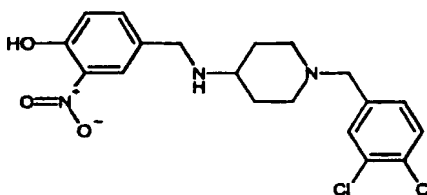
5 **5-((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-2-methoxyphenol**



MS: APCI(+ve) 395 (M+1)

**Example 15**

10 **4-((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-2-nitrophenol**

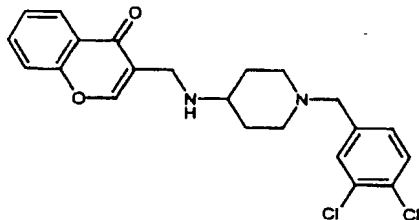


MS: APCI(+ve) 410 (M+1)

**Example 16**

15 **3-((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-4H-chromen-4-one**

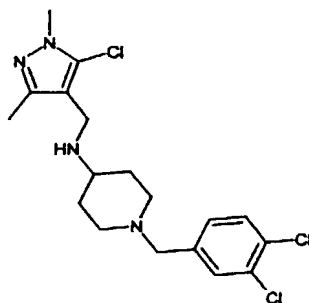
32



MS: APCI(+ve) 417 (M+1)

**Example 17**

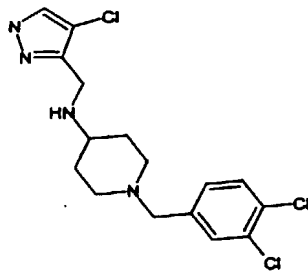
- 5 **N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine**



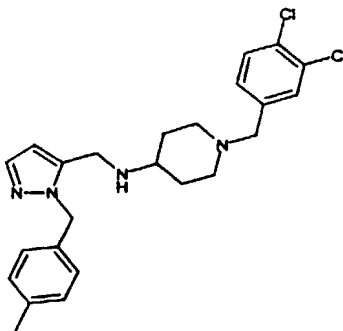
MS: APCI(+ve) 403 (M+1)

10 **Example 18**

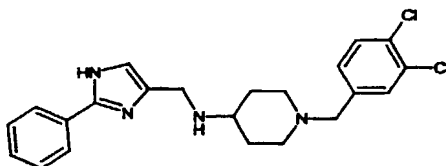
- N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine**



MS: APCI(+ve) 373 (M+1)

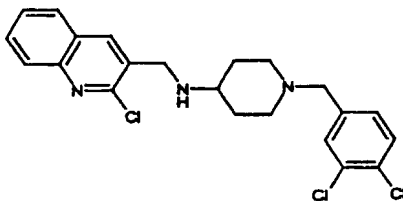
**Example 19****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-([1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl)amine**

5 MS: APCI(+ve) 443 (M+1)

**Example 20****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-((2-phenyl-1H-imidazol-4-yl)methyl)amine**

10

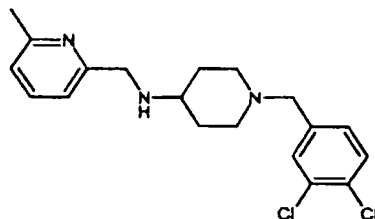
MS: APCI(+ve) 414 (M+1)

**Example 21****N-((2-Chloro-3-quinoliny)methyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine**

15

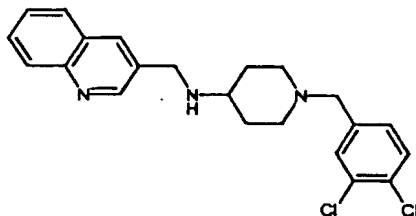
MS: APCI(+ve) 434 (M+1)



**Example 22****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine**

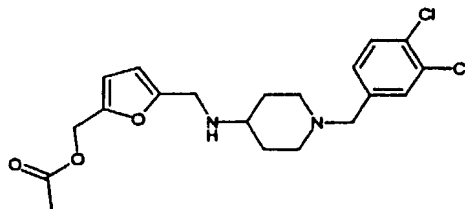
MS: APCI(+ve) 364 (M+1)

5

**Example 23****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine**

MS: APCI(+ve) 400 (M+1)

10

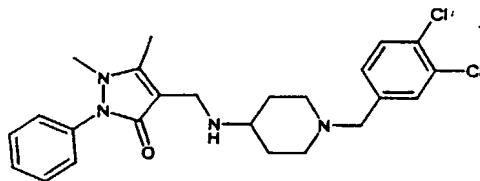
**Example 24****[5-({1-(3,4-Dichlorobenzyl)-4-piperidinyl}amino)methyl]-2-furyl)methyl acetate**

MS: APCI(+ve) 411 (M+1)

15

**Example 25**

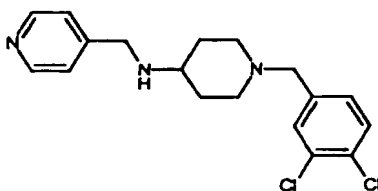
**4-(((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one**



5 MS: APCI(+ve) 459 (M+1)

**Example 26**

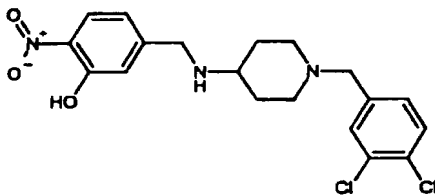
**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine**



10 MS: APCI(+ve) 350 (M+1)

**Example 27**

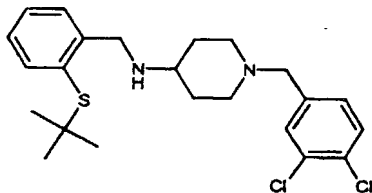
**5-(((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-2-nitrophenol**



15 MS: APCI(+ve) 410 (M+1)

**Example 28**

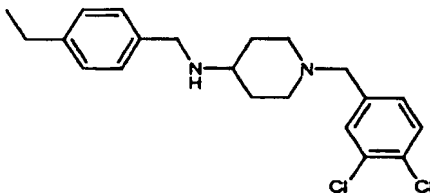
**N-[2-(tert-Butylsulfonyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine**



MS: APCI(+ve) 437 (M+1)

**Example 29**

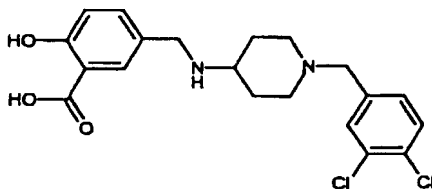
- 5 **N-[(1-(3,4-Dichlorobenzyl)-4-piperidinyl)-N-(4-ethylbenzyl)amine]**



MS: APCI(+ve) 377 (M+1)

**Example 30**

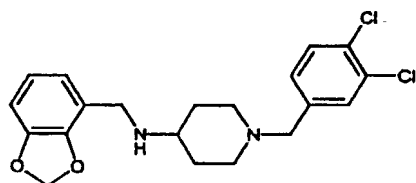
- 10 **5-([(1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino]methyl)-2-hydroxybenzoic acid**



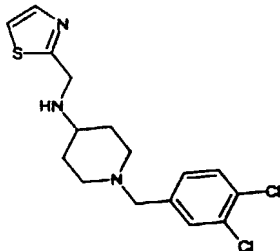
MS: APCI(+ve) 409 (M+1)

**Example 31**

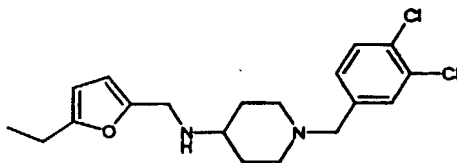
- 15 **N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine**



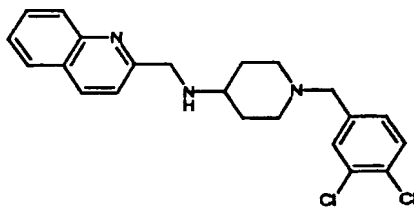
MS: APCI(+ve) 393 (M+1)

**Example 32****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(1,3-thiazol-2-ylmethyl)amine**

5 MS: APCI(+ve) 356 (M+1)

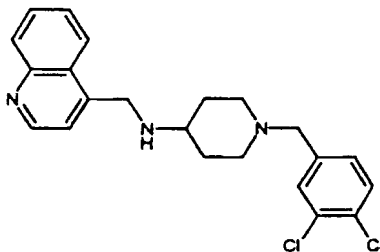
**Example 33****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-[(5-ethyl-2-furyl)methyl]amine**

10 MS: APCI(+ve) 367 (M+1)

**Example 34****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(2-quinolinylmethyl)amine**

15 MS: APCI(+ve) 400 (M+1)

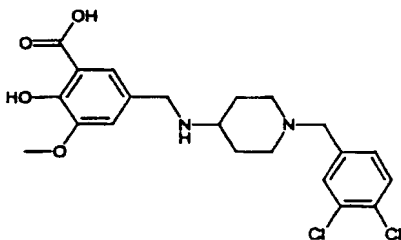
**Example 35****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(4-quinolinylmethyl)amine**



MS: APCI(+ve) 400 (M+1)

**Example 36**

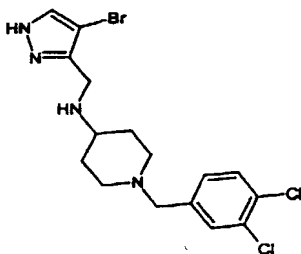
- 5 **5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid**



MS: APCI(+ve) 439 (M+1)

10 **Example 37**

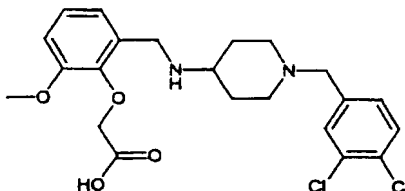
- N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine**



MS: APCI(+ve) 419 (M+1)

15 **Example 38**

**2-[2-(((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-6-methoxyphenoxy]acetic acid**

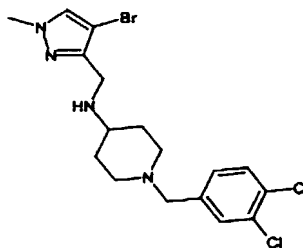


MS: APCI(+ve) 453 (M+1)

5

**Example 39**

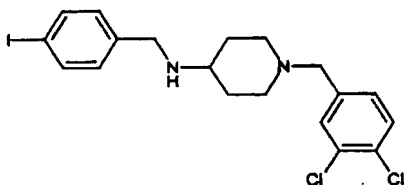
**N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine**



10 MS: APCI(+ve) 433 (M+1)

**Example 40**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine**

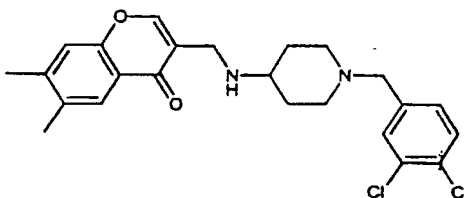


15 MS: APCI(+ve) 475 (M+1)

**Example 41**

**3-(((1-(3,4-Dichlorobenzyl)-4-piperidinyl)amino)methyl)-6,7-dimethyl-4H-chromen-4-one**

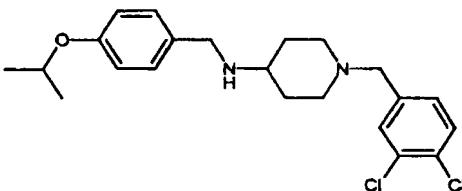
40



MS: APCI(+ve) 445 (M+1)

**Example 42**

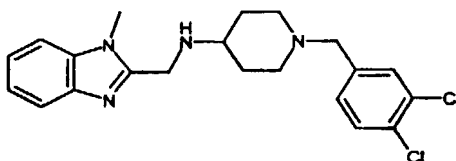
- 5
- N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine**



MS: APCI(+ve) 407 (M+1)

**Example 43**

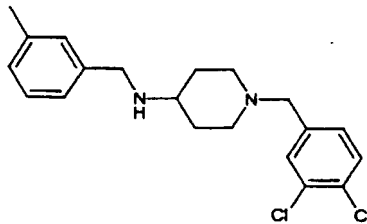
- 10
- N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine**



MS: APCI(+ve) 403 (M+1)

- 15
- Example 44**

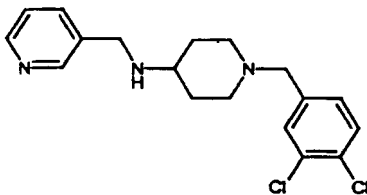
**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine**



MS: APCI(+ve) 363 (M+1)

**Example 45**

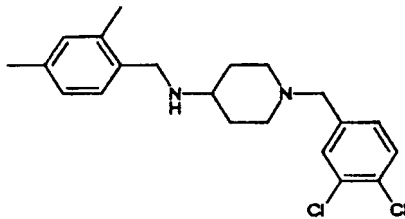
5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine**



MS: APCI(+ve) 350 (M+1)

**Example 46**

10 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine**



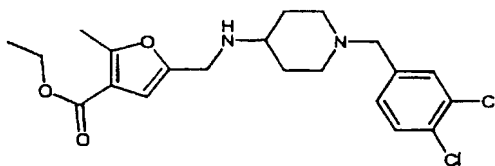
MS: APCI(+ve) 377 (M+1)

**Example 47**

15 **Ethyl 5-(((1-(3,4-dichlorobenzyl)-4-piperidinyl)amino)methyl)-2-methyl-3-furoate**



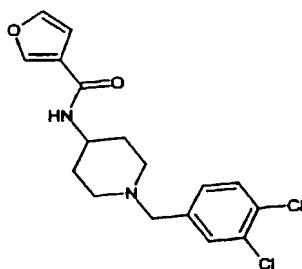
42



MS: APCI(+ve) 425 (M+1)

**Examples 48-73****(i) Examples 48-73**

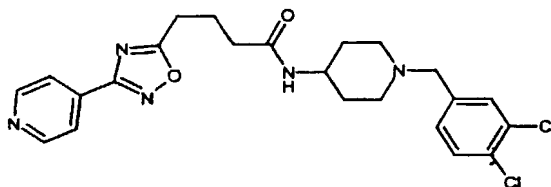
Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (2 equiv) was added to a solution of the product from Example 1 step (ii) (hydrochloride salt) (1mg), the appropriate acid (2 equivalents) and diisopropylethylamine (5 equivalents) in dimethylformamide (0.17ml) and was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.3ml).

**Example 48****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide**

MS: APCI(+ve) 353 (M+1)

**Example 49****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide**

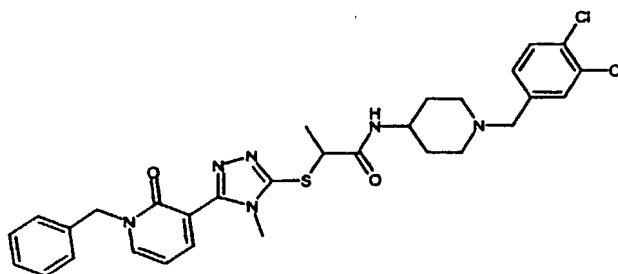
43



MS: APCI(+ve) 474 (M+1)

**Example 50**

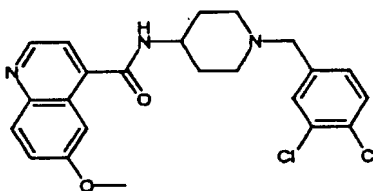
- 5 **2-[[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide**



MS: APCI(+ve) 611 (M+1)

10 **Example 51**

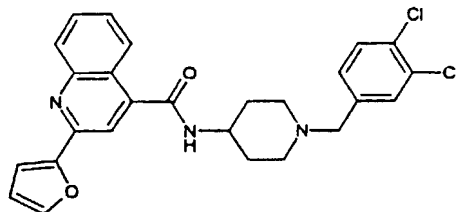
- N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide**



MS: APCI(+ve) 444 (M+1)

15 **Example 52**

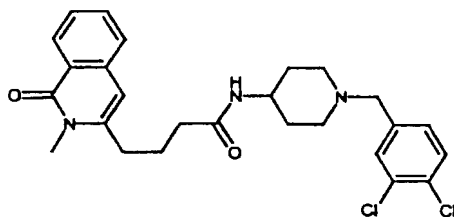
- N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide**



MS: APCI(+ve) 480 (M+1)

**Example 53**

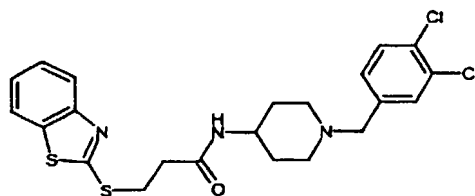
- 5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide**



MS: APCI(+ve) 486 (M+1)

10 **Example 54**

- 3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]propanamide**



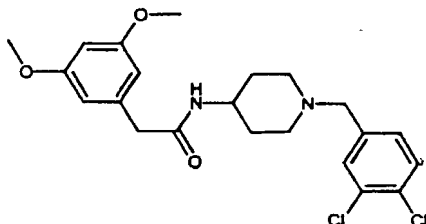
MS: APCI(+ve) 480 (M+1)

15

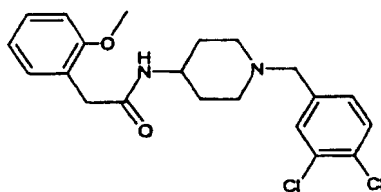
**Example 55**

- N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(3,5-dimethoxyphenyl)acetamide**

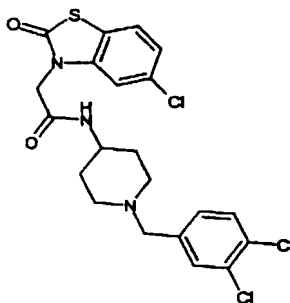
45



MS: APCI(+ve) 437 (M+1)

**Example 56**5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(2-methoxyphenyl)acetamide**

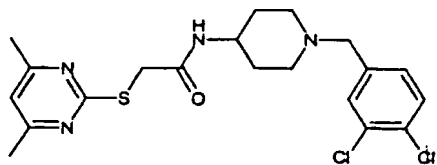
MS: APCI(+ve) 407 (M+1)

**Example 57**10 **2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide**

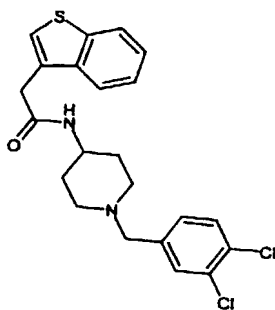
MS: APCI(+ve) 486 (M+1)

15 **Example 58****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfonyl]acetamide**

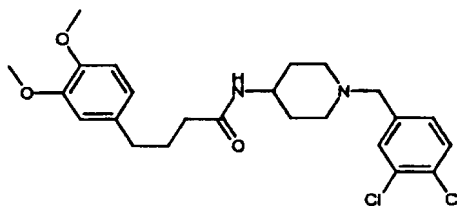
46



MS: APCI(+ve) 439 (M+1)

**Example 59**5 **2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide**

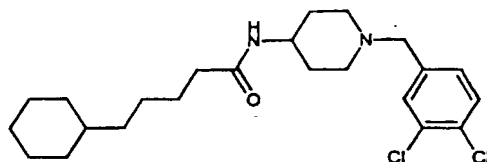
MS: APCI(+ve) 433 (M+1)

**Example 60**10 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide**

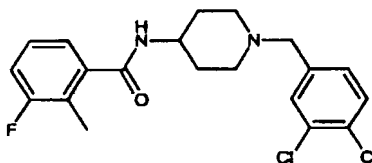
MS: APCI(+ve) 465 (M+1)

**Example 61**15 **5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide**

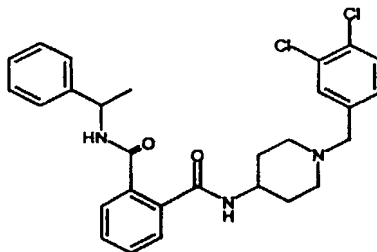
47



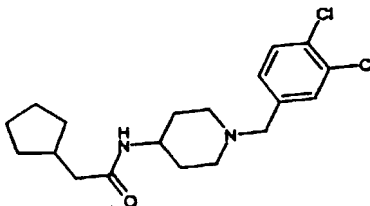
MS: APCI(+ve) 425 (M+1)

**Example 62**5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide**

MS: APCI(+ve) 395 (M+1)

**Example 63**10 **N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(1-phenylethyl)phthalamide**

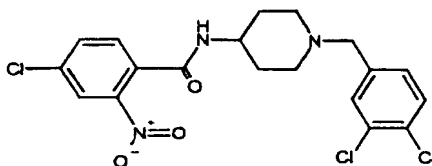
MS: APCI(+ve) 510 (M+1)

**Example 64**15 **2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide**

MS: APCI(+ve) 369 (M+1)

**Example 65**

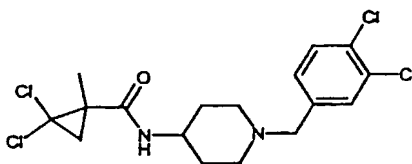
**4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-nitrobenzamide**



MS: APCI(+ve) 444 (M+1)

**Example 66**

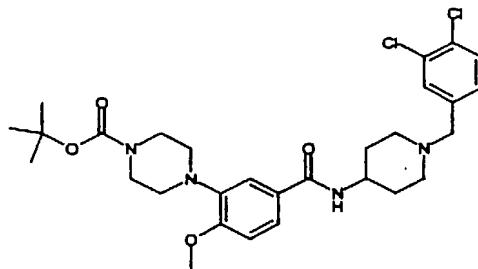
**2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-1-methylcyclopropanecarboxamide**



MS: APCI(+ve) 411 (M+1)

**Example 67**

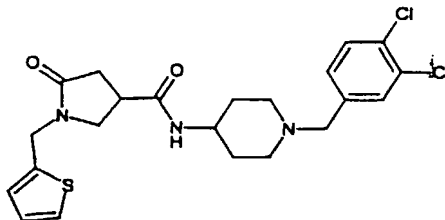
**tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidiny]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate**



MS: APCI(+ve) 577 (M+1)

**Example 68**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide**

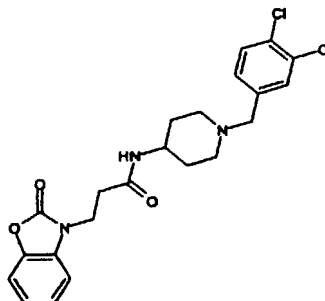


MS: APCI(+ve) 466 (M+1)

5

**Example 69**

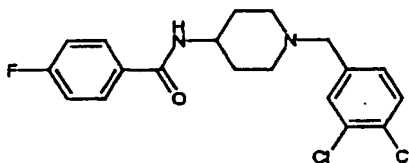
**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide**



10 MS: APCI(+ve) 448 (M+1)

**Example 70**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide**

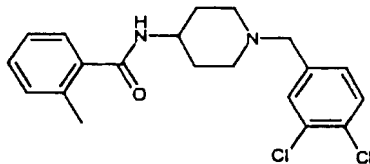


15 MS: APCI(+ve) 381 (M+1)

**Example 71**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide**

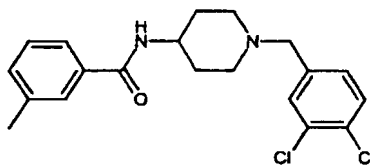




MS: APCI(+ve) 377 (M+1)

**Example 72**

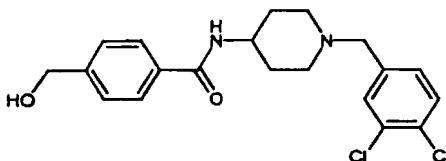
- 5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide**



MS: APCI(+ve) 377 (M+1)

**Example 73**

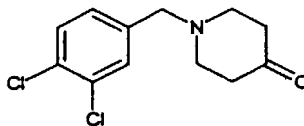
- 10 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide**



MS: APCI(+ve) 393 (M+1)

**Examples 74-93**

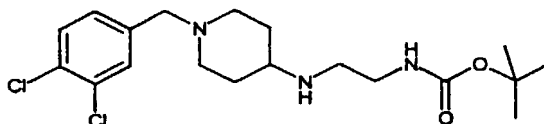
- 15 **(i) 1-(3,4-Dichlorobenzyl)-4-piperidinone**



A solution of 3,4-dichlorobenzyl chloride (2.8ml), 4-ketopiperidine hydrochloride monohydrate and triethylamine (8ml) in dimethylformamide (30ml) was stirred at room temperature for 20h. The mixture was partitioned between water and ethyl acetate, the

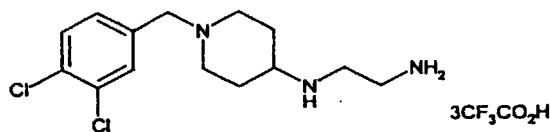
organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 40-50% ethyl acetate/isohexane. Yield 2.1g.  
MS: APCI(+ve) 258/60 (M+1)

5 (ii) **tert-Butyl 2-{{1-(3,4-dichlorobenzyl)-4-piperidinyl}amino}ethylcarbamate**



A solution of the product from step (i) (1.61g), N-(tert-butoxycarbonyl)-ethylenediamine (1g) and sodium triacetoxyborohydride (2.12g) in dichloromethane (20ml) was stirred at room temperature for 3h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Yield 1.28g.  
10 MS: APCI(+ve) 402/4 (M+1)

(iii) **N-1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine, tri-trifluoroacetate salt**



15 The product from step (ii) (1.28g) was treated with trifluoroacetic acid (5ml) in dichloromethane (10ml). After 20h, the solution was evaporated, the residue triturated with ether and the solid (1.62g) collected.  
MS: APCI(+ve) 302/4 (M+1)

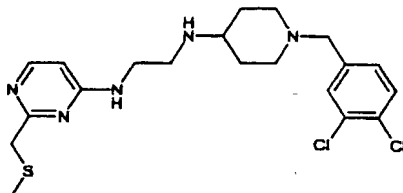
20

(iv) **Examples 74-93**

The product from step (iii) (0.0026g), the appropriate activated halo-aromatic (1.25 equivalents) and diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrrolidinone (0.15ml) was heated at 100°C for 20h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).  
25

**Example 74**

**N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-{2-[(methylsulfonyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine**

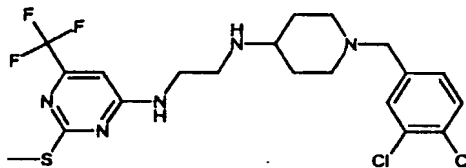


MS: APCI(+ve) 440(M+1)

5

**Example 75**

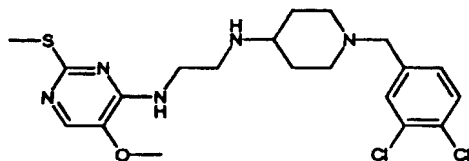
**N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[2-(methylsulfonyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine**



10 MS: APCI(+ve) 494(M+1)

**Example 76**

**N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-[5-methoxy-2-(methylsulfonyl)-4-pyrimidinyl]-1,2-ethanediamine**



15

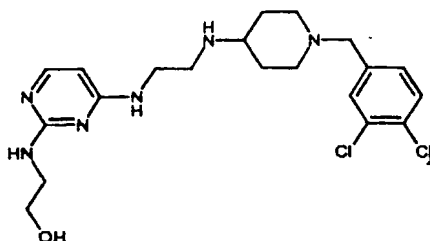
MS: APCI(+ve) 456(M+1)

**Example 77**

**2-((4-((2-([1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino)ethyl)amino)-2-pyrimidinyl)amino)-1-ethanol**

20

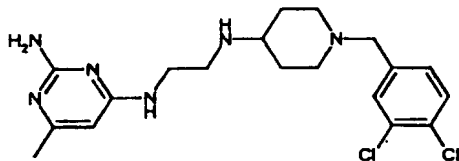
53



MS: APCI(+ve) 439(M+1)

**Example 78**

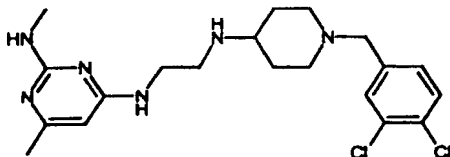
- 5 **N<sup>4</sup>-(2-([1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino)ethyl)-6-methyl-2,4-pyrimidinediamine**



MS: APCI(+ve) 409(M+1)

10 **Example 79**

- N<sup>4</sup>-(2-([1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino)ethyl)-N<sup>2</sup>,6-dimethyl-2,4-pyrimidinediamine**

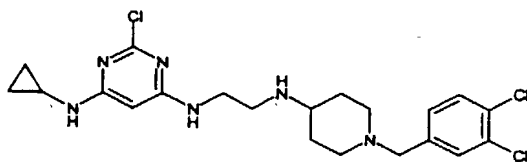


MS: APCI(+ve) 423(M+1)

15

**Example 80**

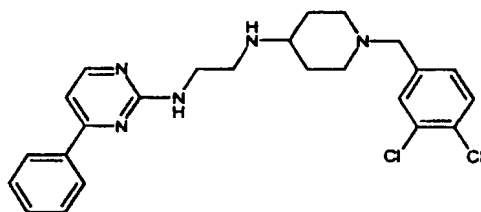
- 2-Chloro-N<sup>4</sup>-cyclopropyl-N<sup>6</sup>-(2-([1-(3,4-dichlorobenzyl)-4-piperidinyl]amino)ethyl)-4,6-pyrimidinediamine**



MS: APCI(+ve) 471(M+1)

**Example 81**

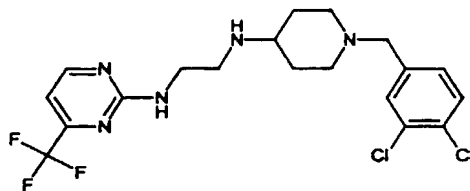
5 **N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine**



MS: APCI(+ve) 456(M+1)

10 **Example 82**

**N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine**



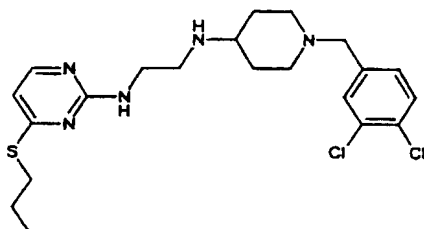
MS: APCI(+ve) 448(M+1)

15

**Example 83**

**N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine**

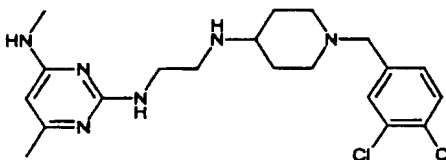
55



MS: APCI(+ve) 454(M+1)

**Example 84**

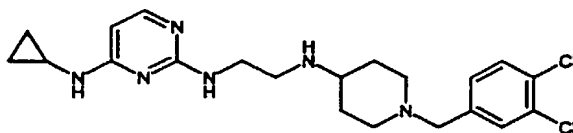
5 **N²-(2-([1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino)ethyl)-N⁴,6-dimethyl-2,4-pyrimidinediamine**



MS: APCI(+ve) 423(M+1)

10 **Example 85**

**N⁴-Cyclopropyl-N²-(2-([1-(3,4-dichlorobenzyl)-4-piperidinyl]amino)ethyl)-2,4-pyrimidinediamine**

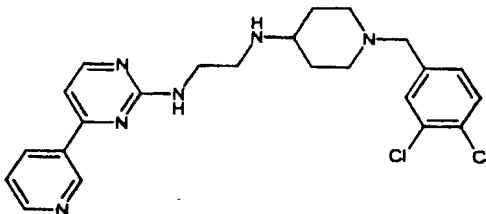


MS: APCI(+ve) 435(M+1)

15

**Example 86**

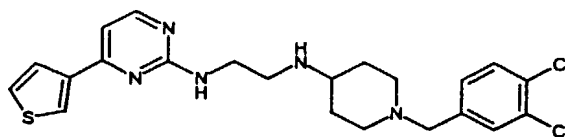
**N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine**



MS: APCI(+ve) 457(M+1)

**Example 87**

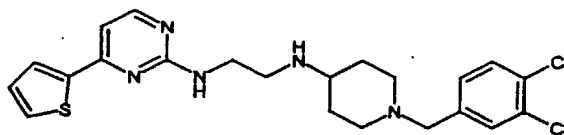
- 5 **N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine**



MS: APCI(+ve) 462(M+1)

10 **Example 88**

- N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine**

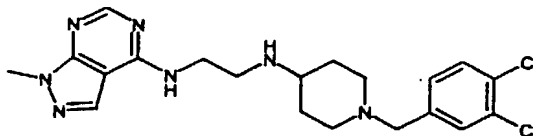


MS: APCI(+ve) 462(M+1)

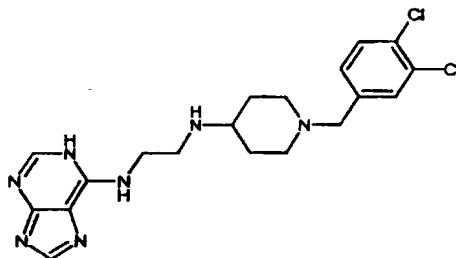
15

**Example 89**

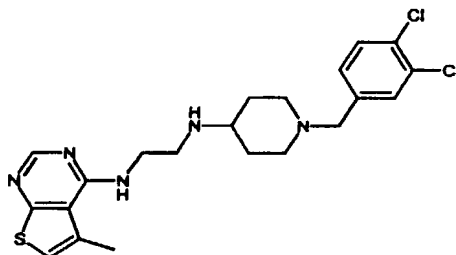
- N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N<sup>2</sup>-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine**



20 MS: APCI(+ve) 434(M+1)

**Example 90****N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(1H-purin-6-yl)-1,2-ethanediamine**

5 MS: APCI(+ve) 420(M+1)

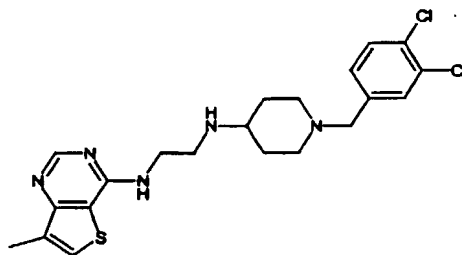
**Example 91****N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine**

10

MS: APCI(+ve) 450(M+1)

**Example 92****N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine**

15

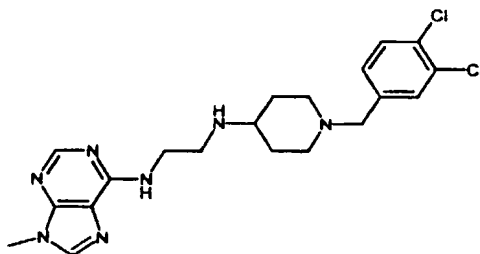




MS: APCI(+ve) 450(M+1)

**Example 93**

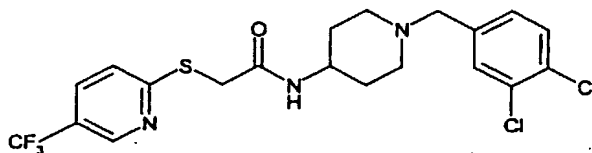
**N<sup>1</sup>-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N<sup>2</sup>-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine**



MS: APCI(+ve) 434(M+1)

**Example 94**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[[5-(trifluoromethyl)-2-pyridinyl]sulfanyl]acetamide**



Carbonyldiimidazole (0.105g) was added to a stirred solution of 2-[[5-(trifluoromethyl)-2-pyridinyl]sulfanyl]acetic acid (0.166g) in dimethylformamide (2ml). After 1h a solution of the product from Example 1 step (ii) (0.3g) in a solution of dimethylformamide and diisopropylethylamine (2 equivalents) (1.5ml) was added and stirred at room temperature for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether and collected. Yield 0.084g as a solid.

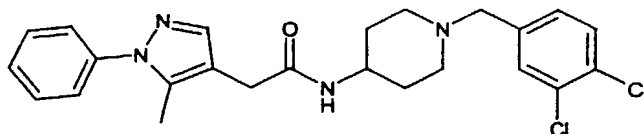
MS: APCI(+ve) 478/80 (M+1)

<sup>1</sup>H NMR: δ (DMSO-d<sub>6</sub>) 8.76(s, 1H), 8.11(d, 1H), 8.02(dd, 1H), 7.59-7.53(m, 3H), 7.29(dd, 1H), 3.91(s, 1H), 3.58-3.45(m, 1H), 3.44(s, 2H), 2.70(br d, 2H), 2.03(br t, 2H), 1.70(br d, 2H), 1.46-1.37(m, 2H).

MP: 98°C

**Example 95**

5 **N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide**



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and of 2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetic acid (0.151g) using the method of Example 94. Yield 0.18g as a solid.

10 MS: APCI(+ve) 457/9 (M+1)

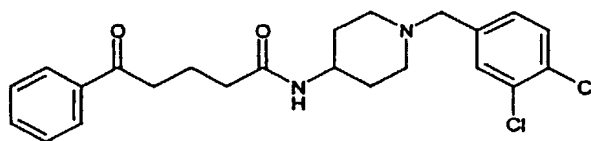
<sup>1</sup>H NMR: δ (DMSO-d<sub>6</sub>) 7.90(d, 1H), 7.59-7.38(m, 8H), 7.29(dd, 1H), 3.54-3.50(m, 1H), 3.45(s, 2H), 3.24(s, 2H), 2.72(br d, 2H), 2.24(s, 3H), 2.03(br t, 2H), 1.72(br d, 2H), 1.46-1.37(m, 2H).

MP: 165°C

15

**Example 96**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide**



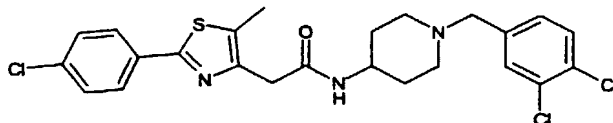
20 The title compound was prepared from the product of Example 1 step (ii) (0.3g) and of 5-oxo-5-phenylpentanoic acid (0.134g) using the method of Example 94. Yield 0.149g as a solid.

MS: APCI(+ve) 433/5 (M+1)

<sup>1</sup>H NMR: δ (DMSO-d<sub>6</sub>) 7.96-7.93(m, 2H), 7.72(d, 1H), 7.65-7.50(m, 5H), 7.28(dd, 1H), 3.57-3.48(m, 1H), 3.44(s, 2H), 3.01(t, 2H), 2.72-2.67(m, 2H), 2.13(t, 2H), 2.04-1.98(m, 2H), 1.86-1.79(m, 2H), 1.69(br s, 2H), 1.41-1.32(m, 2H).

25

MP: 130°C

**Example 97****2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide**

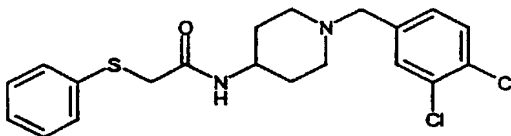
5

The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[2-(4-chlorophenyl)-5-methyl-1,3-thiazol-4-yl]acetic acid (0.187g) using the method of Example 94. Yield 0.1g as a solid.

MS: APCI(+ve) 510/2 (M+1)

10  $^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 8.00(d, 1H), 7.85-7.82(m, 2H), 7.59-7.52(m, 4H), 7.29(dd, 1H), 3.57-3.51(m, 3H), 3.44(s, 2H), 2.72(br d, 2H), 2.41(s, 3H), 2.06(t, 2H), 1.73(br d, 2H), 1.48-1.38(m, 2H).

MP: 170°C

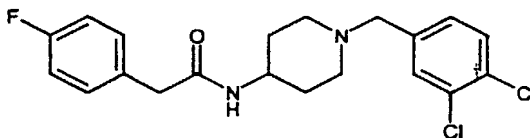
**15 Example 98****N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide**

20 The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-(phenylsulfanyl)acetic acid (0.118g) using the method of Example 94. Yield 0.056g as a solid.

MS: APCI(+ve) 409 (M+1)

$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 8.00(d, 1H), 7.57(d, 1H), 7.53(d, 1H), 7.36-7.27(m, 5H), 7.20-7.16(m, 1H), 3.61(s, 2H), 3.55-3.47(m, 1H), 3.44(s, 2H), 2.69-2.66(m, 2H), 2.02(t, 2H), 1.67-1.64(m, 2H), 1.41-1.31(m, 2H).

25 MP: 97-99°C

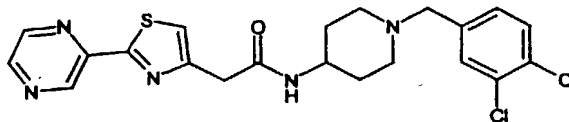
**Example 99****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(4-fluorophenyl)acetamide**

The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-(4-fluorophenyl)acetic acid (0.108g) using the method of Example 94. Yield 0.15g as a solid.

MS: APCI(+ve) 395 (M+1)

<sup>1</sup>H NMR: δ (DMSO-d<sub>6</sub>) 7.98(d, 1H), 7.57(d, 1H), 7.53(d, 1H), 7.30-7.25(m, 3H), 7.13-7.07(m, 2H), 3.54-3.48(m, 1H), 3.45(s, 2H), 3.37(s, 2H), 2.72-2.69(m, 2H), 2.02(t, 2H), 1.71-1.68(m, 2H), 1.44-1.34(m, 2H).

MP: 144-7°C

**Example 100****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-[2-(2-pyraziny)-1,3-thiazol-4-yl]acetamide**

The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetic acid (0.155g) using the method of Example 94. Yield 0.08g as a solid.

MS: APCI(+ve) 462 (M+1)

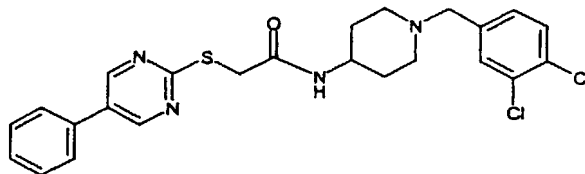
<sup>1</sup>H NMR: δ (DMSO-d<sub>6</sub>) 9.25(d, 1H), 8.74-8.71(m, 2H), 8.07(d, 1H), 7.64(s, 1H), 7.59-7.54(m, 2H), 7.31-7.28(m, 1H), 3.69(s, 2H), 3.59-3.54(m, 1H), 3.45(s, 2H), 2.74-2.71(m, 2H), 2.04(t, 2H), 1.76-1.74(m, 2H), 1.49-1.39(m, 2H).

MP: 186-9°C

**Example 101**

**N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide**

62



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetic acid (0.172g) using the method of Example 94.

Yield 0.115g as a solid.

5 MS: APCI(+ve) 487/9 (M+1)

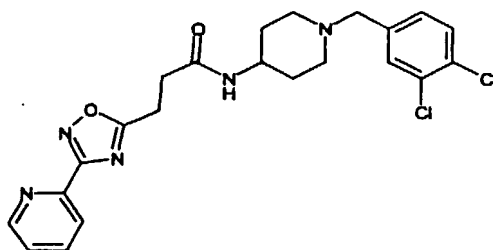
$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 8.96(s, 2H), 8.09(d, 1H), 7.78-7.75(m, 2H), 7.58-7.43(m, 5H), 7.28(dd, 1H), 3.91(s, 2H), 3.59-3.52(m, 1H), 3.44(s, 2H), 2.70(br d, 2H), 2.03(br t, 2H), 1.72(br d, 2H), 1.47-1.38(m, 2H).

MP: 157°C

10

#### Example 102

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide**

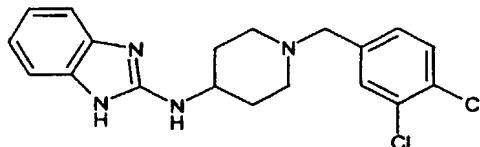


15 The title compound was prepared from the product of Example 1 step (ii) (0.9g) and 3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.3g) using the method of Example 94. Yield 0.074g as a solid.

MS: APCI(+ve) 460/2 (M+1)

$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 8.76-8.74(m, 1H), 8.05-7.99(m, 2H), 7.94(d, 1H), 7.61-7.56(m, 20 2H), 7.52(d, 1H), 7.28(dd, 1H), 3.56-3.48(m, 1H), 3.43(s, 2H), 3.19(t, 2H), 2.71-2.66(m, 4H), 2.03(t, 2H), 1.69(br d, 2H), 1.42-1.33(m, 2H).

MP: 155°C

**Example 103****N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-1H-benzimidazol-2-amine**

5

**(i) Ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate**

A solution of 2-chlorobenzimidazole (1g) and ethyl 4-amino-1-piperidinecarboxylate (2g) in 1-methyl-2-pyrrolidinone was heated at 130°C for 24h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 1% triethylamine/5% methanol in dichloromethane. Yield 0.630g as a solid.

10 TOF MS ES+ 289.1652 (M+1)

**(ii) N-(4-Piperidiny)-1H-benzimidazol-2-amine, dihydrochloride salt**

15 The product from step (i) (0.58g) was heated under reflux with 5M hydrochloric acid (20ml) for 24h. The solvent was evaporated under reduced pressure, the residue azeotroped with toluene, washed with ether. Yield 0.58g as a solid.

TOF MS ES+ 217.1452 (M+1)

**(iii) N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-1H-benzimidazol-2-amine**

20 Triethylamine (0.223ml) was added to a stirred suspension of the product from step (ii) (0.2g) in dimethylformamide. After 5min 3,4-dichlorobenzaldehyde (0.175g) then sodium triacetoxyborohydride (0.212g) was added and the mixture stirred at room temperature for 3h. The mixture was partitioned between 2M hydrochloric acid and ether, the aqueous layer was basified with aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. The residue was triturated with ethyl acetate/ether and the solid collected. Yield 0.045g.

25 TOF MS ES+ 375.4257 (M+1)

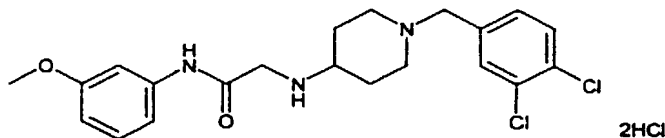
$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 10.6(br s, 1H), 7.60-7.56(m, 2H), 7.32(dd, 1H), 7.12-7.09(m, 2H), 6.86-6.83(m, 2H), 6.49(d, 1H), 3.55-3.49(m, 3H), 2.79-2.71(m, 2H), 2.13-1.91(m, 4H), 1.56-1.46(m, 2H).

MP: 125°C

5

#### Example 104

**2-[[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino]-N-(3-methoxyphenyl)acetamide, dihydrochloride salt**



10 2-Chloro-N-(3-methoxyphenyl)-acetamide (0.241g) was added to a stirred solution of the product of Example 1 step (ii) (dihydrochloride salt) (0.4g), triethylamine (0.608g) in 1-methyl-2-pyrrolidinone (5ml). The reaction mixture was heated at 80°C for 6h then partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried and evaporated under reduced pressure. Purification was by chromatography eluting

15 with chloroform/isohexane/triethylamine/methanol 30:15:3:0.5. The resulting product was converted to the hydrochloride salt using ethereal hydrogenchloride. Yield 0.135g.

TOF MS ES+ 422.1406 (M+1)

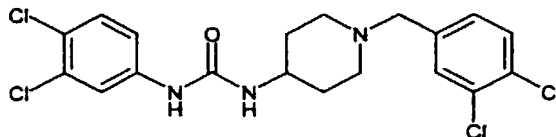
$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 11.21(br s, 1H), 10.82(s, 1H), 9.53(br s, 2H), 7.95(s, 1H), 7.75(d, 1H), 7.60(d, 1H), 7.31-7.23(m, 2H), 7.15(d, 1H), 6.70(dd, 1H), 4.28(br s, 2H), 3.97(br ,

20 H), 3.73(s, 3H), 2.96(br, 2H), 2.28-2.05(m, 4H).

MP: 274-6°C

#### Example 105

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea**



25

3,4-Dichlorophenyl isocyanate (0.081g) was added to a stirred solution of the product from Example 1 step (ii) (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure.

Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid.

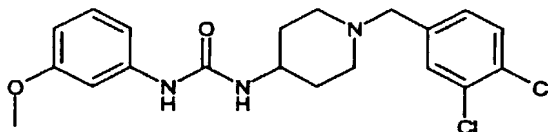
TOF MS ES+ 446.0360 (M+1)

$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 8.65(s, 1H), 7.82(d, 1H), 7.59(d, 1H), 7.54(s, 1H), 7.31(d, 1H), 7.22(dd, 1H), 6.26(d, 1H), 3.45(br s, 3H), 2.67(m, 2H), 2.11(m, 2H), 1.81(m, 2H), 1.40(m, 2H).

MP: 189-190°C

#### Example 106

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea**



3-Methoxyphenyl isocyanate (0.064g) was added to a stirred solution of the product from Example 1 step (ii) (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure.

Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid.

MS: APCI(+ve) 408/10 (M+1)

$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 8.32(s, 1H), 7.59(d, 1H), 7.55(d, 1H), 7.31(dd, 1H), 7.13(m, 1H), 7.09(d, 1H), 6.83(dd, 1H), 6.47(dd, 1H), 6.09(d, 1H), 3.69(s, 3H), 3.46(m, 3H), 2.66(m, 2H), 2.13(m, 2H), 1.81(m, 2H), 1.42(m, 2H).

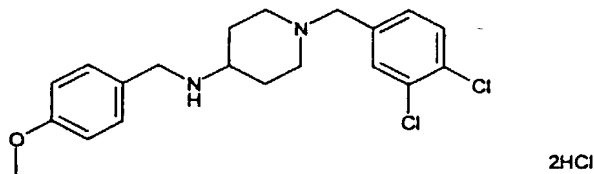
MP: 178-9°C

#### Example 107

**N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt**



66



The title compound was prepared from the product of Example 1 step (ii) (0.185g) and 4-methoxybenzaldehyde (0.49ul) using the method of Example 1 step (i). Yield 0.84g as a solid.

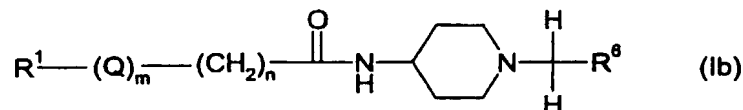
5 MS: APCI(+ve) 379/81 (M+1)

$^1\text{H NMR}$ :  $\delta$  (DMSO- $d_6$ ) 11.33(br s, 1H), 9.56(br s, 2H), 7.96 (s, 1H), 7.74(d, 1H), 7.61(d, 1H), 7.52(d, 1H), 6.97(d, 1H), 4.27(s, 2H), 4.07(s,2H), 3.77(s, 3H), 3.39-2.94(m, 5H), 2.32-2.28(m, 2H), 2.15-2.07(m, 2H).

MP: >250°C

10

The following table lists Examples 108-348 which are of compounds of formula (I) all of which accord to formula (Ib).



| Example | R <sup>1</sup>                                   | (Q) <sub>m</sub> | n | R <sup>6</sup>                                     |
|---------|--|------------------|---|--|
| 108     | phenyl   | m=0              | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 109     | 4-Br-C <sub>6</sub> H <sub>4</sub>               | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 110     | 4-NH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 111     | 2-Br-C <sub>6</sub> H <sub>4</sub>               | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 112     | 4-F-C <sub>6</sub> H <sub>4</sub>                | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 113     | 3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 114     | 2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 115     | 3-Cl-4-OH-C <sub>6</sub> H <sub>3</sub>          | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 116     | 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 117     | 2-Cl-C <sub>6</sub> H <sub>4</sub>               | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 118     | 4-Cl-C <sub>6</sub> H <sub>4</sub>               | m=0              | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

|     |   |     |   |  |
|-----|---|-----|---|--|
| 119 | 3,4-(OH) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 120 | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 121 | phenyl  | m=0 | 4 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 122 | 3,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 123 | 3-F-4-OH-C <sub>6</sub> H <sub>3</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 124 | 3,4-methylenedioxyphenyl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 125 | 4-OH-C <sub>6</sub> H <sub>4</sub>  | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 126 | 4-OH-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 127 | 4-phenyl-phenyl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 128 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 129 | 3-OH-C <sub>6</sub> H <sub>4</sub>  | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 130 | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>  | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 131 | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  | m=0 | 3 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 132 | 3,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 133 | C <sub>6</sub> F <sub>5</sub>   | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 134 | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 135 | 4-OCF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 136 | 3,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | m=0 | 3 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 137 | 4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 138 | 4-N(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>                                     | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 139 | 4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>   | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 140 | 3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>                                 | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 141 | 3,4-methylenedioxyphenyl  | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 142 | 3-NH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 143 | naphth-1-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 144 | 3-OCH <sub>3</sub> -4-OH-C <sub>6</sub> H <sub>3</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 145 | 3-(6-Br-1-(prop-2-en-1-yl)-naphth-2-yloxymethyl)phenyl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 146 | 4-(4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> O)-C <sub>6</sub> H <sub>4</sub> | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

|     |   |     |   |  |
|-----|---|-----|---|--|
| 147 | 3-F-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>                               | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 148 | 3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                                    | m=0 | 4 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 149 | 3-OH-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 150 | 4-(C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> O)-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 151 | 4-(3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> )-C <sub>6</sub> H <sub>4</sub> | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 152 | 2,5-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 153 | 4-I-C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 154 | 3-Br-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 155 | 2-CH <sub>3</sub> -3-NO <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                 | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 156 | 3-OH-4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>                              | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 157 | 3-F-C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 158 | 2-F-C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 159 | 3,5-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                 | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 160 | 3-Cl-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 161 | phenyl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 162 | 3,5-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 163 | 3-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                                   | m=0 | 2 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 164 | 2,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 165 | 2-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                                   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 166 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 167 | 3,5-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 168 | Pyridin-3-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 169 | Pyridin-2-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 170 | 5-Br-pyridin-3-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 171 | 2,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                 | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 172 | 4-(benzyloxy)phenyl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 173 | 3-(benzyloxy)phenyl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 174 | 2-methyl-naphth-1-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 175 | 2-CH <sub>3</sub> CH <sub>2</sub> O-C <sub>6</sub> H <sub>4</sub>                   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 176 | 3,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                 | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 177 | 4-CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

|     |   |     |   |  |
|-----|---|-----|---|--|
| 178 | Indol-1-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 179 | 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>                                  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 180 | Thien-2-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 181 | 3-Cl-4-OH-C <sub>6</sub> H <sub>3</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 182 | 2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 183 | 2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 184 | 2-Br-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 185 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 186 | 3-Br-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 187 | 3,5-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                 | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 188 | 3-NH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>                                  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 189 | 2-(ClCH <sub>2</sub> C(O)NH)-<br>thiazol-4-yl                                     | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 190 | 3-Cl-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 191 | 2,5-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>               | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 192 | 4-OH-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 193 | Indol-3-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 194 | 5-OCH <sub>3</sub> -indol-3-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 195 | Naphth-2-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 196 | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                                  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 197 | 3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>             | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 198 | 4-CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 199 | 4-S(O) <sub>2</sub> CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 200 | 2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>              | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 201 | 4-F-C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 202 | 2-(pyrazin-2-yl)-thiazol-4-<br>yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 203 | 2-CH <sub>3</sub> -5-(CH <sub>3</sub> ) <sub>2</sub> CH-indol-<br>3-yl            | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 204 | 5-(pyrrolidin-1-yl)-<br>tetrazol-2-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

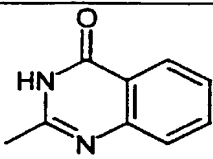
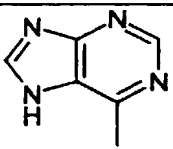
|     |   |     |   |  |
|-----|---|-----|---|--|
| 205 | 5-(4-CH <sub>3</sub> -phenyl)-tetrazol-2-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 206 | 3,5-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 207 | 3-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 208 | 5-Cl-benzo[b]thiophen-3-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 209 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 210 | 2-phenyl-5-methyl-thiazol-4-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 211 | 4-OCF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 212 | 3-methyl-5-Cl-benzo[b]thiophen-2-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 213 | 3-methyl-benzo[b]thiophen-2-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 214 | 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 215 | 3-NO <sub>2</sub> -1,2,4-triazol-1-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 216 | 3,4-(NO <sub>2</sub> ) <sub>2</sub> -5-CH <sub>3</sub> -pyrazol-1-yl                                | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 217 | 4-(CH <sub>3</sub> ) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>2</sub> O-C <sub>6</sub> H <sub>4</sub> | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 218 | 2,3-(CH <sub>3</sub> ) <sub>2</sub> -indol-5-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 219 | 3,5-(CH <sub>3</sub> ) <sub>2</sub> -4-Cl-pyrazol-1-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 220 | 3,5-(CH <sub>3</sub> ) <sub>2</sub> -4-NO <sub>2</sub> -pyrazol-1-yl                                | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 221 | 2,4-(NO <sub>2</sub> ) <sub>2</sub> -imidazol-1-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 222 | 4-NO <sub>2</sub> -imidazol-1-yl  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 223 | 3,5-(CH <sub>3</sub> ) <sub>2</sub> -pyrazol-1-yl   | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 224 | 4-CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> -C <sub>6</sub> H <sub>4</sub>                    | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 225 | 2-CN-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 226 | 4-Cl-C <sub>6</sub> H <sub>4</sub>  | O   | 1 | 4-Cl-C <sub>6</sub> H <sub>4</sub>                 |
| 227 | 4-Cl-C <sub>6</sub> H <sub>4</sub>  | O   | 1 | 2-Br-C <sub>6</sub> H <sub>4</sub>                 |

|     |                                    |     |   |   |
|-----|------------------------------------|-----|---|---|
| 228 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 3-(CO <sub>2</sub> CH <sub>3</sub> )-4-Br-C <sub>6</sub> H <sub>4</sub>   |
| 229 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  |
| 230 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 3-benzoyl-phenyl  |
| 231 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 5-OCH <sub>3</sub> -benzimidazol-2-yl   |
| 232 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 4-Br-C <sub>6</sub> H <sub>4</sub>  |
| 233 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 4-(1,2,3-thiadiazol-4-yl)-phenyl  |
| 234 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>  |
| 235 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 4-(2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> )CH <sub>2</sub> S(O) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> |
| 236 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 3,5-Br <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 237 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | Indan-5-yl  |
| 238 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 2-F-3-Cl-C <sub>6</sub> H <sub>3</sub>  |
| 239 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | benzofurazan-5-yl   |
| 240 | 4-Cl-C <sub>6</sub> H <sub>4</sub> | O   | 1 | 7-Cl-quinolin-2-yl  |
| 241 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 2,5-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 242 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 2,3-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 243 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 4-F-C <sub>6</sub> H <sub>4</sub>   |
| 244 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3-CO <sub>2</sub> CH <sub>3</sub> -4-Br-C <sub>6</sub> H <sub>3</sub>   |
| 245 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  |
| 246 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3-benzoyl-phenyl  |
| 247 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 4-CH <sub>3</sub> -naphth-1-yl  |
| 248 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3,4-methylene-dioxyphenyl   |
| 249 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 5-OCH <sub>3</sub> -benzimidazol-2-yl   |
| 250 | 4-F-C <sub>6</sub> H <sub>4</sub>  | m=0 | 1 | 3-NO <sub>2</sub> -4-CH <sub>3</sub> -  |

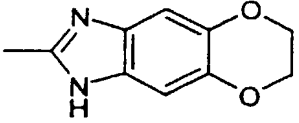
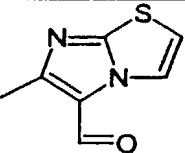
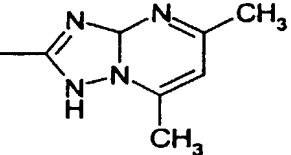
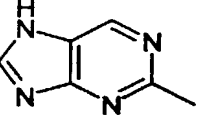
|     |   |     |   |   |
|-----|---|-----|---|---|
|     |   |     |   | C <sub>6</sub> H <sub>3</sub>   |
| 251 | 4-F-C <sub>6</sub> H <sub>4</sub>         | m=0 | 1 | 3,4-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 252 | 4-F-C <sub>6</sub> H <sub>4</sub>         | m=0 | 1 | 3-CH <sub>3</sub> -4-OCH <sub>3</sub> -<br>C <sub>6</sub> H <sub>3</sub>  |
| 253 | 4-F-C <sub>6</sub> H <sub>4</sub>         | m=0 | 1 | 4-(2-C(O)NH <sub>2</sub> -<br>C <sub>6</sub> H <sub>4</sub> )-C <sub>6</sub> H <sub>4</sub>                                     |
| 254 | 4-F-C <sub>6</sub> H <sub>4</sub>         | m=0 | 1 | 4-Br-C <sub>6</sub> H <sub>4</sub>  |
| 255 | 4-F-C <sub>6</sub> H <sub>4</sub>         | m=0 | 1 | 4-(2,6-Cl <sub>2</sub> -<br>C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> S(O) <sub>2</sub> -<br>C <sub>6</sub> H <sub>4</sub> |
| 256 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 4-Cl-C <sub>6</sub> H <sub>4</sub>  |
| 257 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 3-Cl-4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 258 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 2,3-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 259 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 4-F-C <sub>6</sub> H <sub>4</sub>   |
| 260 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>  |
| 261 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  |
| 262 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 3-benzoyl-phenyl  |
| 263 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 3,4-methylene-<br>dioxyphenyl   |
| 264 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 3,5-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 265 | 3-(pyridin-2-yl)-1,2,4-<br>oxadiazol-5-yl | m=0 | 2 | 3-NO <sub>2</sub> -4-CH <sub>3</sub> -<br>C <sub>6</sub> H <sub>3</sub>   |
| 266 | 3-(pyridin-2-yl)-1,2,4-                   | m=0 | 2 | 3,4-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |

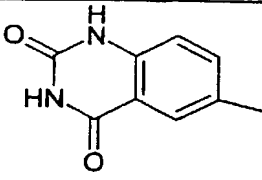
|     |  |     |   |  |
|-----|--|-----|---|--|
|     | oxadiazol-5-yl   |     |   |  |
| 267 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                     |
| 268 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 3-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> |
| 269 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 4-Br-C <sub>6</sub> H <sub>4</sub>                                   |
| 270 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | Indan-5-yl   |
| 271 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                     |
| 272 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | Naphth-2-yl  |
| 273 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                     |
| 274 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | benzofurazan-5-yl  |
| 275 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                    |
| 276 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 7-Cl-quinolin-2-yl   |
| 277 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 3-Cl-C <sub>6</sub> H <sub>4</sub>                                   |
| 278 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                     |
| 279 | 3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl                  | m=0 | 2 | 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                     |
| 280 | 4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>      | O   | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                   |
| 281 | 4-Cl-C <sub>6</sub> H <sub>4</sub>                     | O   | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                   |
| 282 | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>       | O   | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                   |
| 283 | 4-NHC(O)CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> | O   | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                   |



|     |   |   |   |  |
|-----|---|---|---|--|
| 284 | 4-O(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>   | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 285 | 3-CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>    | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 286 | 2-C(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                   | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 287 | 2-NHC(O)CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                              | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 288 | 3,5-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                 | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 289 | 2-OCH <sub>3</sub> -5-NO <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 290 | 4-CN-C <sub>6</sub> H <sub>4</sub>  | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 291 | 2-Cl-5-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>                               | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 292 | 2-NO <sub>2</sub> -5-CH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>                 | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 293 | 3-Cl-5-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>                              | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 294 | 3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>                                    | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 295 | 3-Br-C <sub>6</sub> H <sub>4</sub>  | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 296 | 4-I-C <sub>6</sub> H <sub>4</sub>   | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 297 | 3,5-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | O | 1 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 298 | 4,6-(NH <sub>2</sub> ) <sub>2</sub> -pyrimidin-2-yl                                 | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 299 | Benzimidazol-2-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 300 | Thiazol-2-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 301 |  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 302 | 5-NO <sub>2</sub> -benzimidazol-2-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 303 | Pyridin-2-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 304 |  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 305 | 1H-1,2,4-triazol-3-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 306 | Pyrimidin-2-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 307 | 1-phenyl-tetrazol-5-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |
| 308 | 4,6-(CH <sub>3</sub> ) <sub>2</sub> -pyrimidin-2-yl                                 | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>  |

|     |   |   |   |   |
|-----|---|---|---|---|
| 309 | 4-(thiophen-2-yl)-<br>pyrimidin-2-yl                                | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 310 | 2-(cyclopropyl-CH <sub>2</sub> S)-<br>1,3,4-thiadiazol-5-yl         | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 311 | 4-methyl-3-(thiophen-2-<br>yl)-1,2,4-triazol-5-yl                   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 312 | 3-CN-6-(CH <sub>3</sub> C(O))-<br>pyridin-2-yl                      | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 313 | 1H-pyrazolo[3,4-<br>d]pyrimidin-4-yl                                | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 314 | 5-OCH <sub>3</sub> -benzimidazol-2-<br>yl                           | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 315 | 5-F-6-Cl-benzimidazol-2-<br>yl                                      | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 316 | 4,5-dihydrothiazol-2-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 317 | 1H-5-phenyl-1,2,4-triazol-<br>3-yl                                  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 318 | 2-(thiophen-2-yl)-1,3,4-<br>oxadiazol-5-yl                          | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 319 | Quinoxalin-2-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 320 | 2,5-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 321 | 2-(pyridin-2-yl)-1,3,4-<br>oxadiazol-5-yl                           | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 322 | 7-CF <sub>3</sub> -quinolin-4-yl                                    | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 323 | 2-(pyridin-2-yl)-4-CH <sub>3</sub> -<br>pyrimidin-6-yl              | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 324 | Naphth-1-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 325 | 3,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 326 | 1,3,4-thiadiazol-2-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 327 | 3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                    | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

|     |   |   |   |   |
|-----|---|---|---|---|
| 328 |    | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 329 | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 330 | 3-CN-5-CH <sub>3</sub> -pyridin-2-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 331 | 4-phenyl-thiazol-2-yl   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 332 |    | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 333 | 2-CH <sub>3</sub> -1,3,4-thiadiazol-5-yl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 334 |   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 335 |  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 336 | 2-phenoxy-phenyl  | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 337 | 2-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                                   | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 338 | 2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>                               | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 339 | 2-CH <sub>3</sub> -6-Cl-C <sub>6</sub> H <sub>3</sub>                               | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 340 | 2-(HC≡C-CH <sub>2</sub> S)-1,3,4-thiadiazol-5-yl                                    | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 341 | 2-CO <sub>2</sub> CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>                    | S | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 342 | 4-CN-C <sub>6</sub> H <sub>4</sub>  | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 343 | 4-((CH <sub>3</sub> ) <sub>2</sub> NCH <sub>2</sub> )-C <sub>6</sub> H <sub>4</sub> | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

|     |   |   |   |   |
|-----|---|---|---|---|
| 344 |  | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 345 | 3-CH <sub>2</sub> OH-C <sub>6</sub> H <sub>4</sub>                                | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 346 | 2-OCH <sub>2</sub> CH <sub>2</sub> OH-C <sub>6</sub> H <sub>4</sub>               | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 347 | 4-CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> O-C <sub>6</sub> H <sub>4</sub> | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |
| 348 | 3-Cl-5-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>                            | O | 1 | 3,4-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> |

#### General Preparation of Examples 108-225

PyBroP® (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 2 equivalents) was added to a solution of the product from Example 1 step (ii) (hydrochloride salt, 1mg) the appropriate acid (2 equivalents) and triethylamine in 1-methyl-2-pyrrolidone (0.2ml) and was left for 24h. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.3ml).

#### General Preparation of Examples 225-240

Step i: *tert*-Butyl 4-[[4-chlorophenoxy]acetyl]amino}-1-piperidinecarboxylate

Prepared following the method of Example 94 using (4-chlorophenoxy)acetic acid (0.50g), 1,1-carbonyldiimidazole (0.50g) and *tert*-butyl 4-amino-1-piperidinecarboxylate (0.46g) to give the subtitle compound (0.54g).

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.34 – 1.40 (2H, m), 1.46 (9H, s), 1.90 – 1.95 (2H, m), 2.86 – 2.88 (2H, m), 4.01 – 4.14 (3H, m), 4.45 (2H, s), 6.38 – 6.41 (1H, m), 6.84 – 6.87 (2H, m), 7.26 – 7.30 (2H, m).

Step ii: 2-(4-chlorophenoxy)-*N*-(4-piperidiny)acetamide

Prepared following the method of Example 1 step (ii) using *tert*-butyl 4-[[4-chlorophenoxy]acetyl]amino}-1-piperidinecarboxylate (0.52g) to give the subtitle compound (0.35g).

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.32 – 1.45 (2H, m), 1.93 – 1.97 (2H, m), 2.68 – 2.77 (2H, m), 3.07 – 3.11 (2H, m), 3.91 – 4.04 (1H, m), 4.45 (2H, s), 6.38 – 6.40 (1H, m), 6.84 – 6.89 (2H, m), 7.26 – 7.31 (2H, m).

## Step iii: Final product

A mixture of the product from step (ii) (1.07mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 241-255

A mixture of 2-(4-fluorophenyl)-*N*-(4-piperidiny)acetamide (WO97/36871; 0.94mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 256-279

Step i: *tert*-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.60g) was dissolved in dichloromethane (10ml). 1,1-Carbonyldiimidazole (0.33g) was added followed by *tert*-butyl 4-amino-1-piperidinecarboxylate hydrochloride (0.5g) and triethylamine (0.31ml). After 2hours water, brine and dichloromethane were added and the phases separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate : methanol (33:1) to give the subtitle compound (0.40g).

<sup>1</sup>H NMR (399.98 MHz, DMSO) δ 1.22 - 1.24 (2H, m), 1.39 (9H, s), 1.62 - 1.71 (2H, m), 2.66 - 2.71 (4H, m), 3.18 - 3.23 (2H, m), 3.65 - 3.83 (3H, m), 7.58 - 7.63 (1H), 8.01 - 8.04 (3H, m), 8.74 - 8.76(1H, m).

Step ii: *N*-(4-Piperidiny)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide  
*tert*-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate (0.40g) was dissolved in dichloromethane (6ml) and trifluoroacetic acid (3ml) was added. After 2hours water, 2N sodium hydroxide and dichloromethane were added and the phases were separated. The organic phase was dried, filtered and evaporated to give the subtitle compound (0.19g).

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.35 – 1.45 (2H, m), 1.86 – 1.97 (2H, m), 2.69 – 2.84 (4H, m), 3.09 – 3.13 (2H, m), 3.32 – 3.36 (2H, m), 3.86 – 3.95 (1H, m), 5.82 – 5.84 (1H, m), 7.42 – 7.45 (1H, m), 7.83 – 7.87 (1H, m), 8.10 – 8.12 (1H, m), 8.78 – 8.79 (1H, m).

Step iii: Final product

- 5 A mixture of the product from step (ii) (1.21mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

10 General Preparation of Examples 280-296

Step i: 2-Chloro-*N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide

Prepared following the general preparation method of Examples 297-357 step (iii) using 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (2.0g), *N,N*-diisopropylethylamine (5.55 ml) and chloroacetyl chloride (0.55ml) to give the subtitle compound (1.0g).

- 15 <sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.48 – 1.61 (2H, m), 1.91 – 1.94 (2H, m), 1.95 – 2.18 (2H, m), 2.77 – 2.80 (2H, m), 3.44 (2H, s), 3.78 – 3.87 (1H, m), 4.04 (2H, s), 7.13 – 7.16 (1H, m), 7.37 – 7.43 (2H, m).

Step ii: Final Product

- 20 A mixture of the product from step (i) (1.34 mg), the appropriate phenol (1.5 equivalents) and potassium *tert*-butoxide (1.4 equivalents) in 1-methyl-2-pyrrolidinone (0.13ml) was left at room temperature for 24hours. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 297-340

- 25 Step i: Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidiny]-, 1,1-dimethylethyl ester

- Carbamic acid, 4-piperidiny-, 1,1-dimethylethyl ester (6.95g) was dissolved in *N,N*-dimethylformamide (70ml). 3,4-Difluorobenzylbromide (4.55ml) and potassium carbonate (16.0g) were added. The mixture was heated to reflux for 16hours, then allowed to cool to room temperature. Ammonium chloride solution was added and the mixture was extracted  
30 thrice with ethyl acetate. The organic phases were washed with water (twice) and brine,

then dried, filtered and evaporated. The residue was triturated with ether : *iso*-hexane (1:1) to give the subtitle compound (8.13g)

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.36 - 1.43 (m, 2H), 1.44 (s, 9H), 1.91 (d, *J* = 11.8 Hz, 2H), 2.08 (td, *J* = 11.4, 2.7 Hz, 2H), 2.75 (d, *J* = 11.3 Hz, 2H), 3.41 (s, 2H), 3.42 - 3.55 (m, 1H), 4.38 - 4.47 (m, 1H), 6.96 - 7.02 (m, 1H), 7.04 - 7.11 (m, 2H), 7.13 - 7.19 (m, 1H)

Step ii: 1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride

Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester was suspended in 6N hydrochloric acid (100ml). After 16hours excess hydrochloric acid was evaporated and the residue azeotroped with toluene, dried and evaporated to give the subtitle compound (8.10g).

<sup>1</sup>H NMR (399.98 MHz, DMSO) δ 1.91-2.01(2H,m), 2.31-2.47(2H,m), 2.86-3.20(2H,m), 3.54-3.66(3H,m), 4.75-4.83(2H,s), 7.26-7.61(3H,m).

Step iii: 2-Chloro-*N*-[1-[(3,4-difluorophenyl)methyl]-piperidin-4-yl]-acetamide

1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride (3.18g) was dissolved in tetrahydrofuran (40ml). Diisopropylethylamine (6.84g) and chloroacetyl chloride (1.33g) were added. After 3hours water, brine and ethyl acetate were added the phase were separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate to give the subtitle compound (0.728g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.46 - 1.59 (2H, m), 1.93 (2H, dt), 2.14 (2H, td), 2.78 (2H, d), 3.43 (2H, s), 3.76 - 3.91 (1H, m), 4.04 (2H, s), 6.39 - 6.51 (1H, m), 6.98 - 7.02 (1H, m), 7.08 (1H, dd), 7.17 (1H, ddd).

Step iv: Final Product

The product from step (iii) (1.21mg) was dissolved in dimethylsulfoxide (50μl) and diisopropylethylamine (1.55mg, 3 equivalents) was added as a solution in dimethylsulfoxide (50μl). The appropriate thiol was added (1 equivalent) in dimethylsulfoxide (40μl) and the reaction mixture was left at room temperature for 24hours. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (400μl).

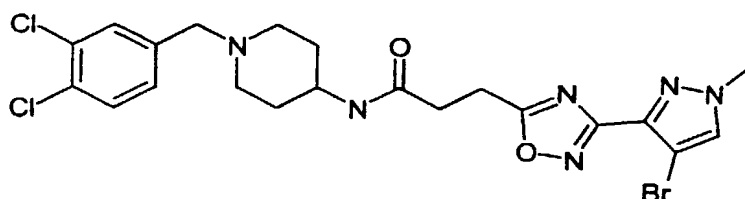
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General Preparation of Examples 341-348

Prepared from the product of general preparation for Examples 297-340 step (iii) and the appropriate phenol following the method of Examples 280-296 step (ii).

**Example 351**

- 5 3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]propanamide



Step i: Methyl 4-[[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]-4-oxobutanoate

- To a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (3.50g) in  
 10 dichloromethane (100ml) was added methyl 4-chloro-4-oxobutanoate (2.00g) dropwise. Triethylamine (3.90g) was added and the reaction stirred under nitrogen for 2 hours. Saturated sodium hydrogen carbonate solution was then added, with the solution being extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over anhydrous magnesium sulfate. After  
 15 filtration the solvent was removed under reduced pressure to leave methyl 4-[[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]-4-oxobutanoate (3.00g).

MS (+veES) 373 ((M+H)<sup>+</sup>)

Step ii: Lithium 4-[[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]-4-oxobutanoate

- To a solution of methyl 4-[[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]-4-oxobutanoate  
 20 (3.72g) in methanol (30ml) was added lithium hydroxide (0.41g) in water (10ml) which was stirred under nitrogen for 48 hours. The solvent was removed under reduced pressure, the residue was triturated with ether and filtered to leave lithium 4-[[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]-4-oxobutanoate (3.50g).

MS (+veES) 359 ((M+H)<sup>+</sup>)

- 25 Step iii: 3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]propanamide

To lithium 4-[[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]-4-oxobutanoate (0.292g) in dichloromethane (6ml) was added dimethylformamide (1.5ml), 1-(3-



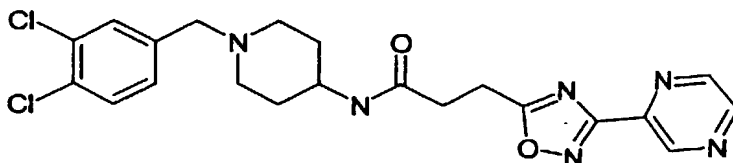
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), 4-bromo-*N*-hydroxy-1-methyl-1*H*-pyrazole-3-carboximidamide (0.175g) and triethylamine (0.161g). Reaction was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure, followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over magnesium sulfate. After filtration the product was azeotroped twice with toluene and was purified by reverse phase hplc (RPHPLC; 75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the titled compound (0.164g).

MS (+veAPC) 543 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO): δ 8.21-8.17(1H,m); 7.95-7.76(1H,m); 7.60-7.54(1H,m); 7.35-7.25(1H,m); 4.35-4.21(1H,m); 3.93(2H,s); 3.44-3.35(2H,m); 3.19-3.14(3H,m); 2.73-2.64(2H,m); 2.58(3H,s); 2.00-1.89(2H,m); 1.73-1.60(2H,m); 1.36-1.24(1H,m).

#### Example 352

*N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]propanamide



To lithium 4-[[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]-4-oxobutanoate (Example 351, step ii) (0.292g) in dichloromethane (6ml) was added *N,N*-dimethylformamide (1.5ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), *N*-hydroxy-2-pyrazinecarboximidamide (0.110g) and triethylamine (0.161g). The reaction mixture was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried

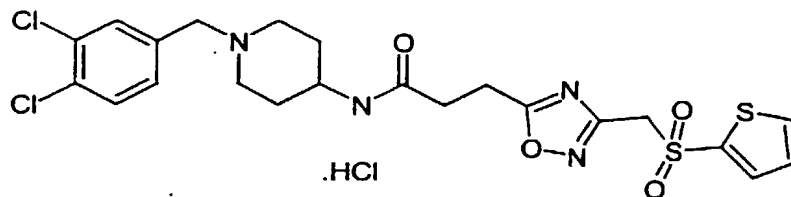
over magnesium sulfate. After filtration the product was azeotroped twice with toluene and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the title compound (0.067g).

MS (+veAPC) 461 ((M+H)<sup>+</sup>)

- 5 <sup>1</sup>H NMR (DMSO) δ 9.23(1H,s); 8.81-8.45(2H,m); 7.96-7.94(1H,m); 7.58-7.56(1H,m); 7.53-7.52(1H,m); 7.29-7.26(1H,m); 3.55-3.48(1H,m); 3.43(2H,s); 3.24-3.20(2H,m); 2.71-2.68(4H,m); 2.03-1.98(2H,m); 1.70-1.68(2H,m); 1.42-1.33(2H,m).

### Example 353

- 10 *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride



- Step i: 3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (1*Z*)-*N*'-hydroxy-2-(2-thienylsulfonyl)ethanimidamide (0.250g) with dihydro-2,5-furandione (0.114g) in dimethylformamide (0.2ml) was heated at 120°C for 2 hours. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave 3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g).

MS (+veES) 303 ((M+H)<sup>+</sup>).

- Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride
- 20 3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g) in dichloromethane was stirred under nitrogen. Oxalyl chloride (0.252g) was added dropwise followed by the addition of one drop of dimethylformamide. After 30 minutes the solvent and oxalyl chloride was removed under reduced pressure followed by the addition of dichloromethane (10ml), 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.347g), and triethylamine (0.202g) and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being
- 25 extracted three times with dichloromethane. The pooled organic phases were washed once

with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a brown oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile) followed by chromatography using 3% ethanol/ dichloromethane. The solvent was removed under reduced pressure, followed by the addition of hydrogen chloride in diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-[3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl]propanamide hydrochloride (0.04g) as a pale yellow solid.

MS (+veES) 545 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 10.51(1H,s); 8.21-8.13(2H,m); 7.91(1H,s); 7.77-7.71(2H,m); 7.58-7.55(1H,m); 7.28-7.26(1H,m); 5.07-5.05(2H,m); 4.26-4.25(2H,m); 3.92(1H,m); 3.34-3.31(2H,m); 3.15-3.08(2H,m); 3.02-2.94(2H,m); 2.60-2.58(2H,m); 1.92-1.84(2H,m); 1.80-1.70(2H,m).

#### Example 354

*N*-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[3-(4-pyridiny)-1,2,4-oxadiazol-5-yl]propanamide

Step i: 3-[3-(4-Pyridiny)-1,2,4-oxadiazol-5-yl]propanoic acid

*N*-hydroxy-4-pyridinecarboximidamide (0.300g) with dihydro-2,5-furandione (0.217g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with ethanol and filtered to leave 3-[3-(4-pyridiny)-1,2,4-oxadiazol-5-yl]propanoic acid (0.241g).

MS (+veES) 220 ((M+H)<sup>+</sup>)

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[3-(4-pyridiny)-1,2,4-oxadiazol-5-yl]propanamide

For method refer to Example 353 step ii.

Purification was performed via chromatography (2.5% ethanol/ dichloromethane). Solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-[3-(4-pyridiny)-1,2,4-oxadiazol-5-yl]propanamide (0.154g) as a pale cream solid.

MS (+veES) 460 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 8.81-8.79(2H,m); 7.96-7.90(3H,m); 7.60-7.56(2H,m); 7.30-7.27(1H,m); 3.53-3.51(1H,m); 3.44(2H,s); 3.23-3.19(2H,m); 2.71-2.68(4H,m); 2.05-1.97(2H,m); 1.71-1.67(2H,m); 1.44-1.32(2H,m).

5 Example 355

Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Step i: Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid

*N*'-hydroxy-2-pyridinecarboximidamide (0.137g) with 3-oxabicyclo[3.1.0]hexane-2,4-dione (0.112g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a  
10 CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.200g).

MS (+veES) 232 ((M+H)<sup>+</sup>)

15 Step ii: Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.139g) and *N,N*'-carbonyldiimidazole (0.110g) in dichloromethane was stirred under nitrogen for 1 hour. 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.198g), and triethylamine  
20 (0.121g) was then added and allowed to stir for 24 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). The solvent was removed under reduced pressure to  
25 leave Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide (0.054g) as a white solid.

MS (+veES) 472 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 8.74-8.73(1H,m); 8.26-8.24(1H,m); 8.03-7.98(2H,m); 7.59-7.55(2H,m); 7.51(1H,s); 7.27-7.25(1H,m); 3.44-3.37(3H,m); 2.67-2.63(3H,m); 2.27-2.21(1H,m); 2.00-1.89(2H,m); 1.66-1.65(2H,m); 1.59-1.56(1H,m); 1.48-1.43(1H,m); 1.37-1.32(2H,m).

Example 356

*N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

5 Step i: 3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid

2-Pyridinecarbohydrazonamide (0.136g) and dihydro-2,5-furandione (0.100g) in 1 ml of dimethylacetamide was heated for 10 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W under nitrogen to leave 3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid in 1ml of dimethylacetamide.

10 MS (-veES) 217 ((M-H)<sup>+</sup>)

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid (0.218g in 1ml dimethylacetamide) and *N,N'*-carbonyldiimidazole (0.250g) in dichloromethane was stirred under nitrogen for  
15 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.316g), and triethylamine (0.218g) was then added and allowed to stir for 2 hours under nitrogen. 1M sodium hydroxide was added to the reaction with the resulting solution being washed three times with dichloromethane. The aqueous phase was acidified with glacial acetic acid, with the water/ acetic acid being removed under reduced pressure. Water was then added  
20 and extracted three times with dichloromethane. The pooled organic phases were extracted once with water and the water removed under reduced pressure to leave a white solid. This was then triturated with diethyl ether/ dichloromethane, filtered and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), solvent removed to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide  
25 (0.02g).

MS (+veES) 459 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO)  $\delta$  8.66-8.65(1H,m); 8.03-8.01(1H,m); 7.95-7.91(1H,m); 7.83-7.81(1H,m); 7.58-7.56(1H,m); 7.52(1H,m); 7.47-7.44(1H,m); 7.29-7.27(1H,m); 3.55-3.50(1H,m); 3.43(2H,s); 2.93-2.89(2H,m); 2.68-2.67(2H,m); 2.55-2.49(2H,m); 2.04-  
30 1.98(2H,m); 1.70-1.68(2H,m); 1.42-1.32(2H,m).

Example 357

*N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide (3-Phenyl-1*H*-1,2,4-triazol-5-yl)acetic acid (0.020g) and *N,N'*-carbonyl diimidazole (0.016g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.031g) and triethylamine (0.036g) was then added and allowed to stir for 1 hour under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to a white solid. This was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Saturated sodium hydrogen carbonate was added to the pooled collected fractions with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide(0.031g).

MS (+veES) 444 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 8.18-8.15(1H,m); 7.98-7.95(2H,m); 7.59-7.54(2H,m); 7.49-7.41(3H,m); 7.31-7.29(1H,m); 3.63(2H,s); 3.57-3.47(1H,m); 3.45(2H,s); 2.74-2.70(2H,m); 2.08-2.01(2H,m); 1.77-1.74(2H,m); 1.48-1.38(2H,m).

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#### Example 358

*N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)propanoic acid (0.175g) and *N,N'*-carbonyldiimidazole (0.148g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.263g), and triethylamine (0.126g) was then added and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was purified by chromatography using 2.5% ethanol/ dichloromethane. The solvent was removed under reduced pressure and was

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purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), followed by 1 ml of glacial acetic acid being added and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate (0.024g).

5 MS (+veES) 445 (M+H)<sup>+</sup>

<sup>1</sup>H NMR (DMSO) δ 8.31-8.29(1H,m); 7.98-7.96(2H,m); 7.66-7.54(5H,m); 7.31-7.29(1H,m); 3.92(2H,s); 3.57-3.56(1H,m); 3.46(2H,s); 2.74-2.71(2H,m); 2.07-2.02(2H,m); 1.78-1.75(2H,m); 1.47-1.39(2H,m).

10 Example 359

*N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Step i: Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate

2-(5-Methyl-1,2,4-oxadiazol-3-yl)pyridine (0.150g) was stirred at -78°C in dry  
15 tetrahydrofuran under nitrogen. (1.6M) *n*-butyl lithium (0.757ml) was added dropwise so as to maintain the temperature at -78°C. After 30 minutes carbon dioxide was passed through the solution and the reaction was allowed to return to room temperature. Once the reaction had reached room temperature, water (1ml) was added and all solvents were removed under reduced pressure to leave a yellow solid. This solid was triturated with  
20 ethyl acetate and filtered to leave a pale yellow solid (0.150g).

<sup>1</sup>H NMR (DMSO+D<sub>2</sub>O) δ 8.75-8.73(1H,m); 8.12-8.00(2H,m); 7.65-7.61(1H,m); 3.77(2H,s).

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

25 Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate (0.140g), 1-(3,4-dichlorobenzyl)-4-piperidinamine (0.170g), PyBroP™ (0.400g) were stirred under nitrogen in dimethylformamide (15ml). *N,N*-Diisopropylethylamine (0.171g) was added and left to stir for 2 hours. 1M sodium hydroxide was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases  
30 were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave product plus dimethylformamide. Water was added which resulted in precipitation of the product. The product was filtered

and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). After removal of the solvent under reduced pressure the resulting white solid was triturated with diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide (0.067g).

5 m.p. 145°C

MS (+veES) 446 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 8.77-8.75(1H,m); 8.37-8.35(1H,m); 8.07-8.00(2H,m); 7.62-7.54(3H,m); 7.31-7.30(1H,m); 4.02(2H,s); 3.60-3.55(1H,m); 3.46(2H,s); 2.74-2.67(2H,m); 2.08-2.03(2H,m); 1.78-1.76(2H,m); 1.48-1.39(2H,m).

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#### Example 360

*N*-[1-(4-Bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 1.00g), 1-bromo-4-(bromomethyl)benzene (1.06g) and potassium carbonate (0.877g) in dimethylformamide (15ml) were heated to 70°C, under nitrogen for 1 hour. Water was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was triturated with diethyl ether, filtered and recrystallised from ethanol/ water to give white crystalline needles of *N*-[1-(4-bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide.

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m.p. 144°C

MS (+veES) 407 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 7.99-7.98(1H,m); 7.51-7.49(2H,m); 7.28-7.24(4H,m); 7.12-7.06(2H,m); 3.51-3.46(1H,m); 3.41(2H,s); 3.36(2H,s); 2.72-2.69(2H,m); 2.01-1.96(2H,m); 1.70-1.68(2H,m); 1.42-1.34(2H,m).

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#### Example 361

2-(4-Fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.05g), 2-quinolinecarbaldehyde (0.033g) and sodium triacetoxyborohydride (0.067g) in dichloroethane (3ml) were stirred under nitrogen for 24 hours. Saturated sodium hydrogen

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carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with diethyl ether/ ethyl acetate and filtered to leave 2-(4-

5 fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide (0.020g).

MS (+veES) 378 ((M+H)<sup>+</sup>)

<sup>1</sup>H NMR (DMSO) δ 8.34-8.31(1H,m); 8.02-7.94(3H,m); 7.75-7.71(1H,m); 7.63-7.55(2H,m); 7.28-7.25(2H,m); 7.13-7.08(2H,m); 3.74(2H,s); 3.57-3.50(1H,m); 3.30(2H,s); 2.79-2.76(2H,m); 2.16-2.11(2H,m); 1.73-1.70(2H,m); 1.48-1.39(2H,m).

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#### Example 362

*N*-[1-(3-Chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.218g) and *N,N'*-

15 carbonyldiimidazole (0.194g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(3-Chloro-4-fluorobenzyl)-4-piperidinamine (JP 59101483; 0.242g) was then

added and left to stir for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over

20 magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with ethyl acetate/ ethanol and filtered to leave *N*-[1-(3-chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide.

m.p. 150°C

MS (+veAPC) 444 ((M+H)<sup>+</sup>)

25 <sup>1</sup>H NMR (DMSO) δ 8.75-8.74(1H,m); 8.05-7.99(2H,m); 7.95-7.93(1H,m); 7.61-7.58(1H,m); 7.48-7.45(1H,m); 7.37-7.30(1H,m); 7.30-7.26(1H,m); 3.53-3.51(1H,m); 3.42(2H,s); 3.21-3.17(2H,m); 2.71-2.66(4H,m); 2.02-1.96(2H,m); 1.70-1.67(2H,m); 1.42-1.33(2H,m).

#### 30 Example 363

*N*-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: *tert*-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate

4-Chloro-3-fluorobenzaldehyde (0.793g) and *tert*-butyl 4-piperidinylcarbamate (1.00g) were stirred under nitrogen in dried tetrahydrofuran (25ml). Sodium triacetoxyborohydride (1.266g) was then added and left for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *tert*-butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) as a white solid.

MS (+veAPC) 343 ((M+H)<sup>+</sup>)

Step ii: 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine

*tert*-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) in dichloromethane (20ml) was stirred under nitrogen. Trifluoroacetic acid (5ml) was then added dropwise and the reaction was left to stir for 2 hours. 1M sodium hydroxide was added to the reaction until basic, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Product purified by chromatography (5% ethanol/ dichloromethane to 10% ethanol/ dichloromethane) and solvent removed under reduced pressure to leave an oil which crystallised over the period of 48 hours. The resulting solid was triturated with diethyl ether and filtered to leave 1-(4-chloro-3-fluorobenzyl)-4-piperidinamine (0.500g) as a white solid.

Step iii: N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.136g) and N,N'-carbonyldiimidazole (0.114g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine (0.150g) was then added and left to stir for 2 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This was triturated with diethyl ether which caused product to crystallise. After filtration, the product was

washed with diethyl ether and dried to N-[1-(4-chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide.

m.p. 132°C

MS (+veES) 444 ((M+H)<sup>+</sup>)

5 <sup>1</sup>H NMR (DMSO) δ 8.76-8.74(1H,m); 8.05-7.99(2H,m); 7.95-7.94(1H,m); 7.61-7.58(1H,m); 7.54-7.50(1H,m); 7.32-7.28(1H,m); 7.16-7.14(1H,m); 3.55-3.47(1H,m); 3.44(2H,s); 3.21-3.17(2H,m); 2.71-2.66(4H,m); 2.03-1.97(2H,m); 1.70-1.67(2H,m); 1.42-1.33(2H,m).

10 Example 364

2-(4-Chlorophenoxy)-N-[1-[(3,4-dichlorophenyl)methyl]-piperidin-4-yl]-acetamide

The product from Example 1 step (ii) was dissolved in dichloromethane (10ml) containing triethylamine (0.081g) and the solution was cooled to 0°C. 4-Chlorophenoxyacetyl chloride (88mg) in dichloromethane (3ml) was added dropwise, the cooling bath was removed and the resulting solution was stirred for 1 hour. Ethyl acetate, water and brine were added and the phases were separated. The organic phase was dried, filtered and evaporated to give an oil which was purified by reverse phase HPLC (with a gradient eluent system (25% MeCN/NH<sub>4</sub>OAc<sub>aq</sub> (0.1%) to 95% MeCN/NH<sub>4</sub>OAc<sub>aq</sub> (0.1%)) to give the title compound (0.049g).

20 <sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 1.51 (2H, ddd), 1.89 - 1.96 (2H, m), 2.15 (2H, td), 2.77 (2H, d), 3.43 (2H, s), 3.85 - 3.96 (1H, m), 4.44 (2H, s), 6.37 (1H, d), 6.85 (2H, dt), 7.14 (1H, dd), 7.26 - 7.29 (2H, m), 7.37 (1H, d), 7.43 (1H, d)

Example 365

25 N-(1-benzyl-4-piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

To a solution of 3-(3-Pyridin-2-yl-[1,2,4]oxadiazol-5-yl)-propionic acid (1g) in tetrahydrofuran (5ml), was added carbonyldiimidazole (0.74g). The mixture was stirred for 10 minutes before addition of 1-benzyl-piperidin-4-ylamine (1ml) in tetrahydrofuran (5ml). The reaction mixture was stirred for 15 minutes then partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was separated, dried (MgSO<sub>4</sub>) and solvent removed by evaporation. Purification by Biotage® 40S eluting 3%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (0.93g).

MS: ESI 392 (+H)

<sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 1.44 (2H, ddd), 1.88 (2H, d), 2.10 (2H, t), 2.73 - 2.78 (2H, m), 2.80 (2H, t), 3.33 (2H, t), 3.46 (2H, s), 3.75 - 3.86 (1H, m), 5.57 (1H, d), 7.23 - 7.32 (5H, m), 7.42 (1H, ddt), 7.84 (1H, tt), 8.10 (1H, dd), 8.79 (1H, td).

5

Example 366

*N*-(2-[[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino]-ethyl)-2-(2-fluoro-phenyl)-acetamide

Step i: (2-Methylamino-ethyl)-carbamic acid *tert*-butyl ester

10 To a solution of (2-amino-ethyl)-carbamic acid-*tert*-butyl ester (5g) and triethylamine (6.5ml) in tetrahydrofuran (1000ml) at 0°C was added methyl iodide (1.94ml) dropwise over a period of 1 hour. The mixture was allowed to warm to ambient temperature and stirred for 72 hours before removal of solvents by evaporation. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried

15 (MgSO<sub>4</sub>) and solvent removed by evaporation to give the title compound (3.7g).

MS: ESI 57((CH<sub>3</sub>)<sub>4</sub>C+), 118 (M+H - (CH<sub>3</sub>)<sub>4</sub>C)

Step ii: (2-[[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino]-ethyl)-carbamic acid *tert*-butyl ester

To a solution of dichlorobenzyl-piperidin-4-one (Example 74, step (i), 4.8g) and acetic acid (1ml) in dichloromethane (100ml) was added (2-methylamino-ethyl)-carbamic acid *tert*-butyl ester (3.26g) and the mixture was stirred for 5 minutes before addition of sodium triacetoxyborohydride (7.9g). The reaction mixture was stirred for 12 hours before addition of sodium bicarbonate solution. The mixture was stirred for ½ hour and then partitioned between water and dichloromethane. The organic layer was separated, dried

25 (MgSO<sub>4</sub>) and solvent removed by evaporation. Purification by Biotage® 40S eluting 10%MeOH/2% triethylamine/dichloromethane gave the title compound (1.7g).

MS: ESI 316/318 (+H - (CH<sub>3</sub>)<sub>4</sub>COCO)

<sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 1.44 (9H, s), 1.50 - 1.60 (4H, m), 1.65 - 1.72 (2H, m), 1.95 (2H, td), 2.23 (3H, s), 2.34 (1H, tt), 2.88 (2H, d), 3.14 - 3.20 (2H, m), 3.41 (2H, s), 4.95 - 5.01 (1H, m), 7.13 - 7.15 (1H, m), 7.37 (1H, d), 7.42 (1H, d).

30

Step iii: *N*<sup>1</sup>-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-*N*<sup>1</sup>-methyl-ethane-1,2-diamine

(2-([1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino)-ethyl)-carbamic acid *tert*-butyl ester (1.7g) was dissolved in 6M HCl (20ml) and stirred for 12 hours. The solvent was evaporated and the residue was azeotroped with toluene and then sodium bicarbonate solution was added. The mixture was stirred for 10 minutes and the product was extracted with dichloromethane. The solvent was removed by evaporation to give the title compound (0.75g).

MS: ESI 316/318 (+H)

Step iv: *N*-(2-([1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino)-ethyl)-2-(2-fluorophenyl)-acetamide

Prepared by the method of Example 359 step (ii) using *N*<sup>1</sup>-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-*N*<sup>1</sup>-methyl-ethane-1,2-diamine and 2-fluorophenylacetic acid.

MS: ESI 452/454 (+H)

<sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 2.08 – 1.94 (2H, m), 2.37 – 2.33 (2H, m), 2.95 (3H, s), 3.18 (2H, t), 3.41 (2H, m), 3.66 – 3.78 (4H, m), 3.75 (2H, s), 3.84 (1H, m), 4.38 (2H, s), 7.16 – 7.28 (2H, m), 7.36 – 7.42 (2H, m), 7.45 (1H, dd), 7.73 (1H, d), 7.72 (1H, d).

#### Example 367

*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-*N*-methyl-2-(4-fluorophenyl)acetamide

Step i: [1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-methyl-amine

To a solution of 1-(3,4-Dichloro-benzyl)-piperidin-4-one (3.1g) in dichloromethane (50ml) and acetic acid (0.69ml) was added methylamine (6ml of a 1M solution in tetrahydrofuran). The mixture was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (3g) and the resulting mixture stirred for 72 hours. Sodium bicarbonate solution (100ml) added and the mixture stirred vigorously for 5 minutes before extraction of the product with dichloromethane (2X200ml). The organics were separated, bulked and dried, (MgSO<sub>4</sub>). Purification by Biotage<sup>®</sup> 40S eluting 10%MeOH/0.5% 880 ammonia/dichloromethane gave the sub-title compound (1.8g).

MS: ESI 273/275 (+H)

<sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 1.36 (2H, qd), 1.82 - 1.91 (2H, m), 2.03 (2H, td), 2.36 (1H, tt), 2.43 (3H, s), 2.76 - 2.83 (2H, m), 3.43 (2H, s), 7.15 (1H, dd), 7.37 (1H, d), 7.42 (1H, d).

Step ii: *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

To a solution of 4-fluorophenylacetic acid (100mg) in tetrahydrofuran (3ml) was added carbonyldiimidazole (105mg). The mixture was stirred for 10 minutes before addition of [1-(3,4-dichlorobenzyl)-piperidin-4-yl]-methyl-amine (177mg) in tetrahydrofuran (2ml). Stirring was continued for 1 hour then solvent removed by evaporation. Purification by  
5 Biotage® 40S eluting 2%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (166mg).

MS: ESI 273/275 (M+H)

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.57 (1H, d), 1.69 (1H, qd), 1.76 - 1.84 (1H, m), 1.88 (1H, q), 2.10  
(2H, td), 2.85 - 2.90 (1H, m), 2.85 (3H, s), 3.42 (2H, s), 3.58 (1H, tt), 3.67 (2H, s), 4.51  
10 (1H, tt), 7.00 (2H, t), 7.11 - 7.15 (1H, m), 7.18 - 7.23 (2H, m), 7.37 (1H, d), 7.41 (1H, dd).

#### Example 368

*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinylloxy)-acetamide

Step i: Ethyl 2-pyrimidinylloxyacetate

15 Ethyl glycolate (1.04g) was dissolved in tetrahydrofuran (10ml) and the solution was cooled to 0°C. Sodium hydride (60% suspension in oil, 0.43g) was added and the suspension was stirred and then sonicated in an ultrasonic bath. 2-Chloropyrimidine (1.14g) was added and the mixture was sonicated for a further 110min. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate, the  
20 organic phases were washed with brine and dried, filtered and evaporated. The residue was purified by chromatography eluting with *iso*-hexane: ethyl acetate (13:7) to give the subtitle compound (1.40g) as an oil.

<sup>1</sup>H NMR (299.944 MHz, CDCl<sub>3</sub>) δ 1.26 (t, *J* = 6.8 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.93 (s, 2H), 6.98 (t, *J* = 4.8 Hz, 1H), 8.53 (d, *J* = 4.8 Hz, 2H).

25 Step ii: 2-Pyrimidinylloxyacetic acid

Ethyl 2-pyrimidinylloxyacetate (1.4g) was dissolved in ethanol (10ml). Sodium hydroxide (2M aq) was added and the mixture was stirred for 64h. The solvent was evaporated and the residue was dissolved in water, filtered and the acidified with concentrated hydrochloric acid. The resulting precipitate was collected and dried to give the subtitle compound  
30 (0.698g).

<sup>1</sup>H NMR (399.98 MHz, DMSO) δ 4.85 (s, 2H), 7.09 (t, *J* = 4.9 Hz, 1H), 8.56 (d, *J* = 4.8 Hz, 2H).

Step iii: *N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinyloxy)-acetamide

The title compound was prepared from the product of Example 1 step (ii) (hydrochloride salt, 335mg) and 2-pyrimidinyloxyacetic acid (170mg) using the method of Example 94.

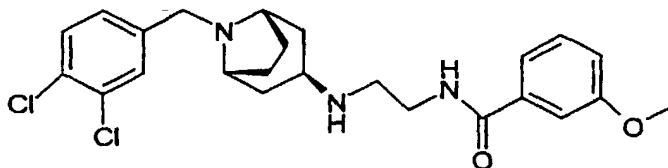
5 Yield 140mg.

m.p. 120-122°C

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.50 (q, J = 11.6 Hz, 2H), 1.91 (d, J = 11.9 Hz, 2H), 2.13 (t, J = 11.1 Hz, 2H), 2.77 (d, J = 11.4 Hz, 2H), 3.42 (s, 2H), 3.86 - 3.95 (m, 1H), 4.87 (s, 2H), 6.49 (d, J = 6.9 Hz, 1H), 7.05 (t, J = 4.9 Hz, 1H), 7.14 (m, 1H), 7.37 (d, J = 8.3  
10 Hz, 1H), 7.42 (s, 1H), 8.57 (d, J=4.8Hz, 2H).

#### Example 369

*N*-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt



15

Step i: 8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one

2,5-Dimethoxytetrahydrofuran (4.92g) was stirred in hydrochloric acid (1M, 25 ml) for 1 hour. 3,4-Dichlorobenzylamine (5ml) was added to hydrochloric acid (1M, 15ml) and the resulting suspension was added to the first solution. Phosphate buffer solution (pH 5.5,  
20 250ml) was added followed by sodium hydroxide (1.6g). A solution of acetone dicarboxylic acid (4.77g) in phosphate buffer solution (pH 5.5, 90ml) was added to the mixture and the solution was stirred. A yellow solid formed and the mixture was left to stand for 64h. The aqueous supernatant was decanted and hydrochloric acid (2.5M) was added to the solid along with ethyl acetate. The layers were separated and the aqueous  
25 phase was extracted twice with dichloromethane containing a little methanol. The organic layers were combined and evaporated to give a crude oil (ca 7g). A portion of the product (ca 2.5g) was purified by chromatography eluting with dichloromethane : methanol (19:1) to give the subtitle compound (1.62g) as a yellow oil.

$^1\text{H}$  NMR (299.944 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62 - 1.70 (m, 2H), 2.09 - 2.15 (m, 2H), 2.23 (d,  $J = 15.9$  Hz, 2H), 2.67 (d,  $J = 16.7$  Hz, 2H), 3.43 - 3.49 (m, 2H), 3.68 (s, 2H), 7.26 (d,  $J = 8.7$  Hz, 1H), 7.41 (d,  $J = 7.5$  Hz, 1H), 7.54 (s, 1H)

Step ii: Carbamic acid, Endo-[2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-1,1-dimethylethyl ester

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (751 mg) and carbamic acid, (2-aminoethyl)-1,1-dimethylethyl ester (520 mg) were dissolved in dichloroethane (23ml). Sodium triacetoxyborohydride (697 mg) was added and the suspension was stirred at room temperature for 20hours. Dichloromethane was added and the solution was washed with sodium bicarbonate solution, then with water and then with brine.

Chromatography of the residue eluting with ethyl acetate : methanol : triethylamine (80:19:1) gave the subtitle compound (688mg) as an oil.

$^1\text{H}$  NMR (399.978 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45 (s, 9H), 1.52 (d,  $J = 14.4$  Hz, 2H), 1.96 - 2.09 (m, 6H), 2.67 (t,  $J = 5.8$  Hz, 2H), 2.88 (t,  $J = 6.4$  Hz, 1H), 3.08 - 3.12 (m, 2H), 3.21 (q,  $J = 5.7$  Hz, 2H), 3.48 (s, 2H), 4.80 - 4.95 (m, 1H), 7.22 (dd,  $J = 8.3, 2.0$  Hz, 1H), 7.37 (d,  $J = 7.9$  Hz, 1H), 7.49 (d,  $J = 2.0$  Hz, 1H)

Step iii: *N*-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt

Carbamic acid, [2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-, 1,1-dimethylethyl ester (337mg) was dissolved in dichloromethane (3ml) and trifluoroacetic acid (3ml) was added. The resulting solution was stirred for 1hour then the volatiles were evaporated. The residue was dissolved in dichloromethane (3ml) and triethylamine (1ml) was added followed by 3-methoxybenzoyl chloride (120 $\mu$ l). The solution was stirred overnight. The solvent was evaporated and the residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). Excess tosic acid in ether was added to the residue and the resultant salt was recrystallised from a mixture of ethyl acetate - ethanol with a little cyclohexane to give the title compound (77mg).

m.p. 180-182.5°C

$^1\text{H}$  NMR (399.98 MHz, DMSO)  $\delta$  2.10 - 2.24 (m, 4H), 2.29 (s, 6H), 2.39 - 2.47 (m, 4H), 3.21 - 3.28 (m, 2H), 3.52 - 3.57 (m, 1H), 3.57 - 3.63 (m, 2H), 3.80 (s, 3H), 3.85 - 3.91 (m, 2H), 4.21 (d,  $J = 5.4$  Hz, 2H), 7.11 (d,  $J = 9.4$  Hz, 4H), 7.13 - 7.18 (m, 1H), 7.38 - 7.45 (m,



3H), 7.48 (d,  $J = 7.9$  Hz, 4H), 7.56 (d,  $J = 6.7$  Hz, 1H), 7.78 (d,  $J = 8.2$  Hz, 1H), 7.84 - 7.90 (m, 1H), 8.38 - 8.52 (m, 2H), 8.81 - 8.87 (m, 1H), 9.44 - 9.51 (m, 1H).

5 Example 370

Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (350mg) was dissolved in  
10 dry methanol (12ml) and ammonium acetate (1g) was added. The mixture was stirred to get partial solution and then sodium cyanoborohydride (106mg) was added. The mixture was heated under reflux for 150 minutes, then allowed to cool to room temperature. The methanol was evaporated, the residue was partitioned between sodium hydroxide and dichloromethane, and the aqueous phase was extracted twice with dichloromethane. The  
15 organic phases were combined, dried, filtered and evaporated to give the subtitle compound.

$[M+H]^+$  (ES+) 285

Step ii: Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

20 3-(2-Pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (305mg) was suspended in dichloromethane (6ml) and oxalyl chloride (0.5ml) was added. The mixture was stirred overnight. Toluene (1ml) was added to the solution, the volatiles were evaporated, then the residue was redissolved in dichloromethane (2ml). Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (all from step(i)) was dissolved  
25 in dichloromethane (4ml) containing triethylamine (0.5ml) and then cooled in an ice bath. The acid chloride solution was added to the amine and the mixture was stirred for 1 hour. Water was added to the reaction mixture and the phases were separated. The aqueous phase was extracted twice with dichloromethane, the organic phases were dried, filtered and evaporated. The residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). The product was suspended  
30 in ether and the ethereal hydrochloric acid was added, the suspension was stirred and then the diethyl ether was evaporated. The residue was dissolved in hot ethyl acetate containing

ethanol and crystallisation was induced by adding *iso*-hexane to give the title compound (47mg).

<sup>1</sup>H NMR (399.98 MHz, DMSO) δ 1.99 - 1.90 (m, 2H), 2.41 - 2.20 (m, 6H), 2.77 (t, J = 6.8 Hz, 2H), 3.23 (t, J = 6.9 Hz, 2H), 3.81 - 3.72 (m, 3H), 4.15 (d, J = 6.2 Hz, 2H), 7.63 - 7.58 (m, 1H), 7.67 (dd, J = 7.6, 2.3 Hz, 2H), 7.76 (d, J = 9.3 Hz, 1H), 8.06 - 7.99 (m, 3H), 8.11 (d, J = 4.1 Hz, 1H), 8.75 (d, J = 4.6 Hz, 1H), 10.13 (t, J = 5.6 Hz, 1H).

Example 371

2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide  
Step i: Methyl (4-acetaminophenoxy)acetate

4-Acetaminophenol (1.51g), potassium carbonate (1.38g) and methyl bromoacetate (1.0ml) were combined in acetone (40ml) and heated to reflux for 5 hours. The mixture was allowed to cool to room temperature, filtered and evaporated. The residue was dissolved in ethyl acetate, washed with water and then with brine then dried, filtered and evaporated to give the subtitle compound (2.32g).

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 2.16 (s, 3H), 3.80 (s, 3H), 4.62 (s, 2H), 6.87 (d, J = 9.1 Hz, 2H), 7.07 (br s, 1H), 7.40 (d, J = 9.0 Hz, 2H)

Step ii: (4-Acetaminophenoxy)acetic acid

Methyl (4-acetaminophenoxy)acetate was hydrolysed following the method of Example 368 step (ii) to give the subtitle compound (1.85g).

<sup>1</sup>H NMR (399.98 MHz, DMSO) δ 2.00 (s, 3H), 4.61 (s, 2H), 6.84 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H), 9.80 (s, 1H).

Step iii: 2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

The title compound was prepared from the product of Example 1 step (ii) (free base, 281mg) and (4-acetaminophenoxy)acetic acid (229mg) using a method hereinbefore described (yield 40mg).

m.p. 177-178.5°C.

<sup>1</sup>H NMR (299.946 MHz, DMSO) δ 1.51 (qd, J = 10.5, 3.7 Hz, 2H), 1.72 - 1.63 (m, 2H), 2.00 (s, 3H), 2.05 (t, J = 3.7 Hz, 2H), 2.77 - 2.68 (m, 2H), 3.45 (s, 2H), 3.70 - 3.57 (m, 1H), 4.39 (s, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.29 (dd, J = 8.1, 1.7 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 1.5 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 9.79 (s, 1H).

Example 372

*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-4-hydroxy-benzeneacetamide

The title compound was prepared from the product of Example 1 step (ii) (free base, 172mg) and 4-hydroxyphenylacetic acid (135mg) using a method hereinbefore described (yield 57mg).

m.p. 72-97°C.

<sup>1</sup>H NMR (399.98 MHz, DMSO) δ 1.37 (q, *J* = 7.0 Hz, 2H), 1.69 (d, *J* = 11.3 Hz, 2H), 2.02 (t, *J* = 5.3 Hz, 2H), 2.71 (d, *J* = 11.3 Hz, 2H), 3.23 (s, 2H), 3.44 (s, 2H), 3.55 - 3.42 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 9.18 (s, 1H).

Example 373

Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (330mg) was dissolved in tetrahydrofuran (5ml) and cooled to 0°C. Lithium tris (3-ethylpentyl-3-oxy)aluminumhydride solution (0.5M, 2.5ml) was added dropwise and the mixture was allowed to attain room temperature overnight. Sodium sulfate decahydrate (ca 2g) was added and the suspension was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate, filtered through kieselguhr and evaporated. The residue was purified by chromatography eluting with dichloromethane: methanol (9:1) to give the subtitle compound 161mg.

<sup>1</sup>H NMR (399.978 MHz, CDCl<sub>3</sub>) δ 1.59 (d, *J* = 8.1 Hz, 2H), 1.64 (t, *J* = 11.4 Hz, 2H), 1.86 - 1.81 (m, 2H), 2.00 - 1.97 (m, 2H), 3.21 - 3.18 (m, 2H), 3.55 (s, 2H), 3.95 (septet, *J* = 5.6 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.50 (s, 1H).

Step ii: Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione

Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol (556mg), phthalimide (321mg) and polymer bound triphenylphosphine (821mg) were combined in tetrahydrofuran (10ml). Diethylazodicarboxylate (330μl) was added and the mixture was

stirred gently overnight. Additional phosphine (0.5g) and diethylazodicarboxylate (200 $\mu$ l) were added and the mixture was stirred for an additional 5 days. The reaction mixture was diluted with ethyl acetate and filtered; the residue was washed with ethyl acetate and methanol. The filtrate was evaporated, and chromatographed eluting with 9:1 ethyl acetate : methanol. RPHPLC of the product (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 100% acetonitrile)) gave the subtitle compound (90mg).  
5  $^1\text{H}$  NMR (399.978 MHz,  $\text{CDCl}_3$ )  $\delta$  1.47 - 1.39 (m, 2H), 1.78 (d,  $J = 7.7$  Hz, 2H), 2.14 - 2.02 (m, 2H), 2.64 (t,  $J = 11.8$  Hz, 2H), 3.36 - 3.25 (m, 2H), 3.92 - 3.81 (m, 2H), 4.56 (septet,  $J = 6.1$  Hz, 1H), 7.41 - 7.32 (m, 2H), 7.59 - 7.55 (m, 1H), 7.74 - 7.69 (m, 2H),  
10 7.86 - 7.82 (m, 2H).

Step iii: Exo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (90mg) was dissolved in ethanol (6ml) containing dichloromethane (3ml); hydrazine hydrate (0.2ml) was added and the resulting solution was stirred at room  
15 temperature for 26hours. The suspension was filtered and the filtrate was evaporated to give the subtitle compound (55mg).

$^1\text{H}$  NMR (399.978 MHz,  $\text{CDCl}_3$ )  $\delta$  1.51 - 1.43 (m, 2H), 1.59 (q,  $J = 4.9$  Hz, 2H), 1.75 - 1.67 (m, 2H), 2.00 - 1.94 (m, 2H), 3.02 - 2.92 (m, 1H), 3.18 - 3.12 (m, 2H), 3.50 (s, 3H), 7.21 (d,  $J = 8.2$  Hz, 1H), 7.37 (d,  $J = 8.2$  Hz, 1H), 7.50 (s, 1H).

20 Step iv: Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following the method of Example 370 step (iii) but without salt formation to give the title compound (15mg).

m.p. 177.5-178°C

25  $^1\text{H}$  NMR (299.946 MHz, DMSO):  $\delta$  1.63 - 1.43 (m, 6H), 1.99 - 1.90 (m, 2H), 2.64 (t,  $J = 7.1$  Hz, 2H), 3.11 - 3.06 (m, 2H), 3.18 (t,  $J = 6.2$  Hz, 2H), 3.49 (s, 2H), 3.97 - 3.83 (m, 1H), 7.32 (dd,  $J = 8.3, 1.9$  Hz, 1H), 7.62 - 7.56 (m, 3H), 7.87 (d,  $J = 8.1$  Hz, 1H), 8.06 - 7.97 (m, 2H), 8.75 (dt,  $J = 3.7, 0.8$  Hz, 1H).

30 Example 374

(R) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

**Step i: (R)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinone**

(R)-(4-Bromophenyl)ethylamine (1.01g) and potassium carbonate (1.45g) were dissolved in a mixture of ethanol (13ml) and water (6ml) and then heated to a vigorous reflux. A solution of 4-hydroxy-4-methoxy-1,1-dimethyl-piperidinium iodide (J. Chem. Soc. Perkin Trans. 2, (1984) 1647) (1.47g) in warm water (6ml) was added dropwise over 40 minutes; reflux was maintained for a further 12 hours, then the reaction was allowed to cool to room temperature. The mixture was evaporated and ethyl acetate and water were added and the phases were separated. The aqueous phase was extracted twice with ethyl acetate, the organic layer was washed with brine, dried, filtered and evaporated. Chromatography of the residue eluting with *iso*-hexane : ethyl acetate (3:2) gave the subtitle compound (804mg).

$^1\text{H NMR}$  (399.978 MHz,  $\text{CDCl}_3$ )  $\delta$  2.66 - 2.80 (m, 4H), 1.38 (d,  $J = 6.9$  Hz, 3H), 2.42 (t,  $J = 6.2$  Hz, 4H), 3.58 (q,  $J = 6.7$  Hz, 1H), 7.24 (d,  $J = 8.5$  Hz, 2H), 7.46 (d,  $J = 9.0$  Hz, 4H).

**Step ii: (R)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinamine**

Prepared following the general method of Example 370 step (i) (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinone (420mg) ammonium acetate (0.80g) and sodium cyanoborohydride (120mg) to give the subtitle compound (449mg).

$^1\text{H NMR}$  (399.978 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J = 6.9$  Hz, 3H), 1.43 - 1.26 (m, 2H), 1.73 (d,  $J = 12.3$  Hz, 1H), 1.81 (d,  $J = 12.6$  Hz, 1H), 2.03 - 1.90 (m, 2H), 2.60 (tt,  $J = 10.6, 5.1$  Hz, 1H), 2.71 (d,  $J = 13.6$  Hz, 1H), 2.94 (d,  $J = 11.3$  Hz, 1H), 3.37 (q,  $J = 6.7$  Hz, 1H), 7.18 (d,  $J = 8.5$  Hz, 2H), 7.43 (d,  $J = 8.2$  Hz, 2H)

**Step iii: (R) N-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide**

Prepared following a method as hereinbefore described using (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinamine (449mg), 3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (0.31g), 1-hydroxybenzotriazole (0.20g), 4-(N,N-dimethylamino)-pyridine (0.13g) and 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (0.30g) to give the title compound (40mg).

m.p. 153-155°C.

$^1\text{H NMR}$  (399.98 MHz, DMSO)  $\delta$  1.23 (d,  $J = 6.7$  Hz, 3H), 1.40 - 1.26 (m, 2H), 1.66 - 1.61 (m, 1H), 1.73 - 1.67 (m, 1H), 1.97 - 1.86 (m, 2H), 2.64 - 2.59 (m, 1H), 2.66 (t,  $J = 7.2$  Hz, 2H), 2.84 - 2.79 (m, 1H), 3.18 (t,  $J = 7.2$  Hz, 2H), 3.42 (q,  $J = 6.4$  Hz, 1H), 3.48 - 3.39 (m,

1H), 7.25 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.59 (ddd, J = 6.7, 4.6, 2.1 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 8.04 - 7.99 (m, 2H), 8.75 (dt, J = 4.4, 1.4 Hz, 1H).

**Example 375**

5 (S) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidiny]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following an analogous series of steps to example 374 but using (S)-(4-bromophenyl)ethylamine to give the title compound.

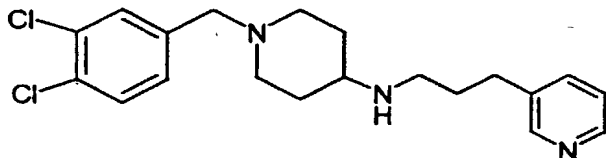
m.p. 141.5-143°C

10  $\alpha_D -29.55^\circ$  (c = 0.13, methanol, 21°C)

<sup>1</sup>H NMR (299.946 MHz, DMSO)  $\delta$  1.23 (d, J = 6.7 Hz, 3H), 1.26 - 1.41 (m, 2H), 1.64 (t, J = 8.1 Hz, 2H), 1.92 (q, J = 11.2 Hz, 2H), 2.58 - 2.67 (m, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.78 - 2.85 (m, 1H), 3.18 (t, J = 7.1 Hz, 2H), 3.37 - 3.46 (m, 1H), 3.42 (q, J = 6.7 Hz, 1H), 7.25 (d, J = 6.7 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.57 - 7.62 (m, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.98 - 8.05 (m, 2H), 8.75 (d, J = 7.5 Hz, 1H).

**Example 385**

1-[3,4-Dichlorobenzyl]-*N*-[3-(3-pyridinyl)propyl]-4-piperidinamine



20 The title compound was prepared from 1-(3,4-dichlorobenzyl)piperidine-4-amine (free base 187mg), 3-(3-pyridinyl)propanal (125mg), sodium triacetoxyborohydride (70mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane (10ml). Water was added, the mixture neutralised with sodium bicarbonate and the organic phase separated, dried and chromatographed on silica with ethyl acetate/methanol (9:1) as eluant, to give the

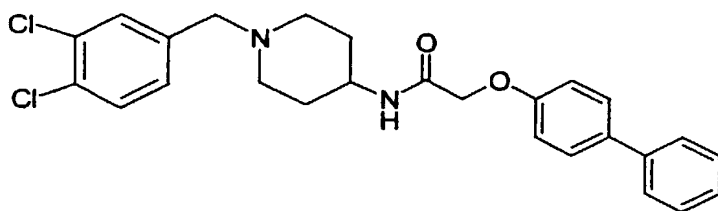
25 title compound (70mg) as a colourless oil.

MS [M+H]<sup>+</sup> (ES+) 378

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.36-1.40 (2H, m), 1.75-1.85 (4H m), 2.0 (2H, t), 2.1-2.2 (2H, m), 2.4-2.45 (1H m), 2.6-2.7 (3H, m), 2.75-2.79 (2H, m), 3.4 (2H, s), 7.1-7.54 (5H, d), 8.44 (2H, m).

5 **Example 386**

2-[(1,1'-Biphenyl)-4-yloxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide

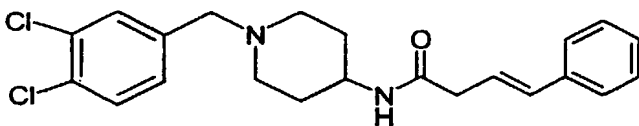


MS  $[\text{M}+\text{H}]^+$  (ES+) 469

10  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.46-1.50 (2H, m), 1.7-1.8 (2H, m), 2.0-2.1 (2H, m), 2.5-2.6 (2H, m), 3.45 (2H, s), 3.65 - 3.7 (1H, m), 4.5 (2H, s), 7.25-7.3 (2H, m), 7.27-7.63 (9H, m), 8.0 (1H, d).

**Example 387**

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-4-phenyl-3-butenamide



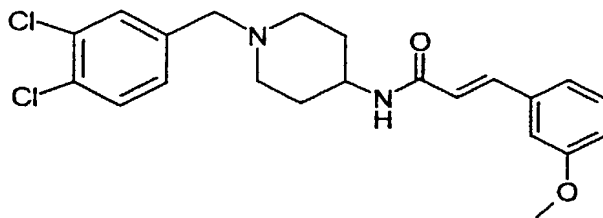
15 MS  $[\text{M}+\text{H}]^+$  (ES+) 403

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.46-1.40 (2H, m), 1.85-1.95 (2H, d), 2.05-2.15 (2H, t), 2.75-2.79 (2H, d), 3.1 (2H, d), 3.4 (2H, s), 3.85-3.95 (1H, m), 5.45 (1H, m), 6.3 (1H, m), 6.5 (1H, d), 7.07-7.43 (8H, m).

20

**Example 388**

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-(3-methoxyphenyl)-2-propenamide.

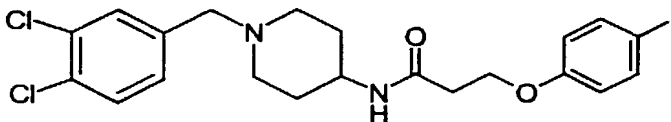


MS [M+H]<sup>+</sup> (ES+) 419

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.46-1.50 (2H, m), 2.0 (2H, m), 2.15-2.25 (2H, m), 2.75-2.85 (2H, m),  
 3.4 (2H, s), 3.8 (3H, s), 3.94-4.05 (1H, m), 5.5 (1H, d), 6.35-6.4 (1H, d), 6.9-7.5 (7H, m),  
 7.6 (1H, d).

**Example 389**

**N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-(4-iodophenoxy)propanamide.**

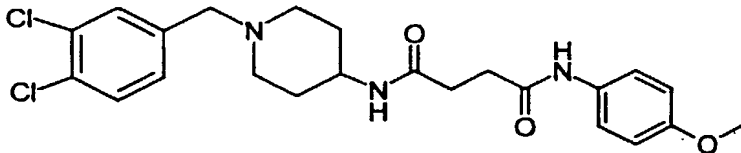


MS [M+H]<sup>+</sup> (ES+) 533

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.46-1.50 (2H, m), 1.9 (2H, d), 2.1-2.2 (2H, t), 2.6 (2H, m), 2.75-2.85  
 (2H, d), 3.4 (2H, d), 3.8-3.9 (1H, m), 4.20 (2H, m), 6.65-6.7 (2H, m), 7.1-7.2 (1H, d), 7.35-  
 7.45 (2H, m), 7.54-7.6 (2H, m).

**Example 390**

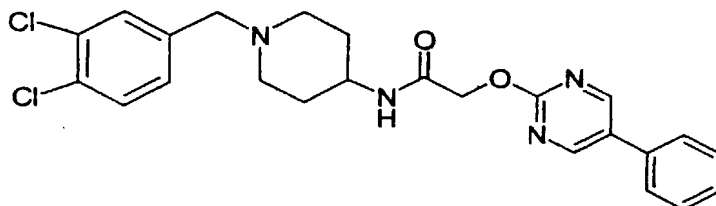
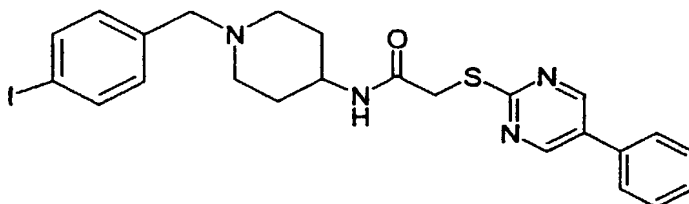
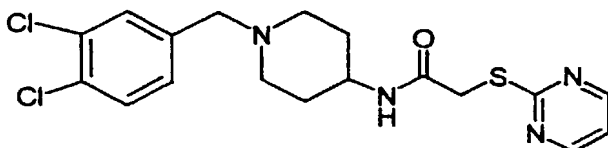
**N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-N'-(4-methoxyphenyl)succinamide**



MS [M+H]<sup>+</sup> (ES+) 464

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.4 (2H, m), 1.6-1.65 (2H, m), 2.05 (2H, m), 2.45 (2H, m), 2.65-2.75  
 (2H, m), 3.0 (2H, m), 3.45 (2H, s), 3.5 (1H, m), 3.7 (3H, s), 5.9 (1H, m), 6.85 (2H, d), 7.3-  
 7.6 (4H, m), 7.7 (1H, d), 9.7 (1H, s).

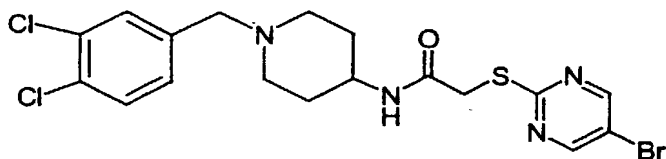


**Example 391****N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-[(5-phenyl-2-pyrimidinyl)oxy] acetamide**5 MS [M+H]<sup>+</sup> (ES+) 471<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.46-1.50 (2H, m), 1.9-2.0 (2H, m), 2.0-2.1 (2H, m), 2.75-2.85 (2H, m), 3.4 (2H, s), 3.9- 4.0 (1H, m), 4.92 (2H, s), 6.53 (1H, d), 7.1-7.6 (7H, m), 7.7 (1H, s), 8.76 (2H, s).10 **Example 392****N-[1-(4-iodobenzyl)-4-piperidiny]-2-(5-phenyl-2-pyrimidinyl)thio]acetamide**MS [M+H]<sup>+</sup> (ES+) 54515 <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.46-1.50 (2H, m), 1.8 (2H, m), 2.1-2.2 (2H, t), 2.65 (2H, m), 3.4 (2H, s), 3.9(3H, m), 6.8 (1H, d), 7.0 (2H, m), 7.5-7.7 (7H, m), 8.8 (2H, d).**Example 393****N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-[(2-pyrimidinyl)thio]acetamide**20 MS [M+H]<sup>+</sup> (ES+) 412

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.46-1.50 (2H, m), 1.8 (2H, m), 2.1 (2H, m), 2.65 (2H, m), 3.4 (2H, s), 3.8 (3H, m), 6.90 (1H, m), 7.05-7.2 (4H, m), 8.58 (2H, d).

**Example 394**

5 **2-[(5-Bromo-2-pyrimidinyl)thio]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide**



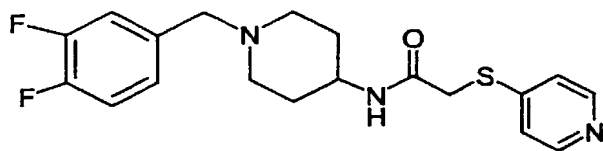
MS  $[\text{M}+\text{H}]^+$  (ES+) 491

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.46 - 1.50 (2H, m), 1.8 (2H, m), 2.15 (2H, m), 2.6 (2H, m), 3.4 (2H, s), 3.8 (3H, m), 6.6 (1H, d), 7.1 (1H, m), 7.3-7.4 (2H, m) 8.58 (2H, d).

10

**Example 395**

**N-[1-(3,4-difluorobenzyl)-4-piperidinyl]-2-(4-pyridinylthio)acetamide**

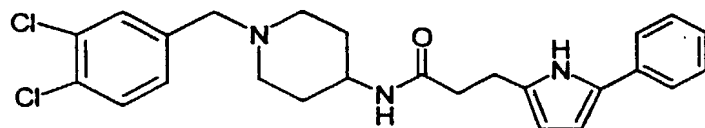


MS  $[\text{M}+\text{H}]^+$  (ES+) 378

15  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.36 - 1.40 (2H, m), 1.8 (2H, m), 2.05 (2H, m), 2.65 (2H, m), 3.4 (2H, m), 3.67 (2H, s), 3.8 (1H, m), 6.5 (1H, m), 6.9-7.24 (4H, m) 8.48 (2H, d).

**Example 396**

**N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(5-phenyl-1H-pyrrol-2-yl)propanamide**



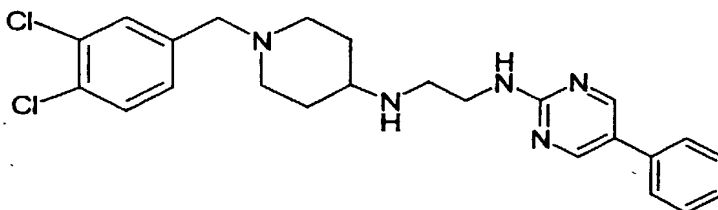
20

MS  $[\text{M}+\text{H}]^+$  (ES+) 454

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.36-1.40 (2H, m), 1.87 (2H, m), 2.05 (2H, m), 2.5 (2H, m), 2.65 (2H, m), 2.96 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 5.35 (1H, d), 5.95-6.0 (1H, m), 6.38 (1H, m), 7.1-7.5 (8H, m), 9.5 (1H, m).

5 **Example 397**

**N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-(5-phenyl-2-pyrimidinyl)-1,2-ethanediamine**



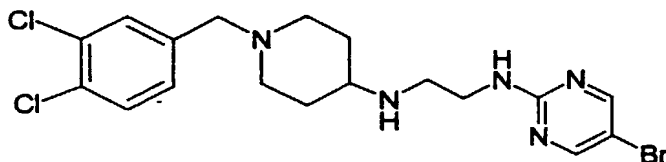
The title compound (20mg) was prepared by heating at reflux  $N^1$ -[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine (100mg) and 2-chloro-5-phenylpyrimidine (100mg) and Hunigs' base (100mg) in toluene for 8 hours. The mixture was purified by chromatography on silica, with ethyl acetate methanol (9:1) as eluant to give the title compound as a yellow oil.

MS  $[\text{M}+\text{H}]^+$  (ES+) 456/8

15  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.51 (2H, m), 1.75 (2H, m), 2.15 (2H, td), 2.9 (2H, m), 3.05 (1H, m), 3.15 (2H, m), 3.44 (2H, m), 3.8 (2H, m), 6.65 (1H, m), 7.0-7.4 (8H, m), 8.5 (2H, m).

**Example 398**

20 **N-[5-bromo-2-pyrimidinyl]-N'-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine**



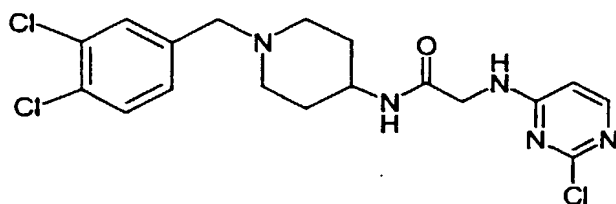
Prepared by the method of Example 397 amine (200mg), 2-chloro-5-bromopyrimidine (130mg), Hunigs' base (200mg) to give the title compound (20mg).

MS  $[\text{M}+\text{H}]^+$  (ES+) 458/60

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.4 (2H, m), 1.75 (2H, m), 2.05 (2H, td), 2.85 (2H, m), 3.0 (1H, m), 3.15 (2H, m), 3.44 (2H, m), 3.75 (2H, m), 6.8 (1H, m), 7.0-7.4 (3H, m), 8.25 (2H, m).

**Example 399**

5 **2-[(2-Chloro-4-pyrimidinyl)amino]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny] acetamide**

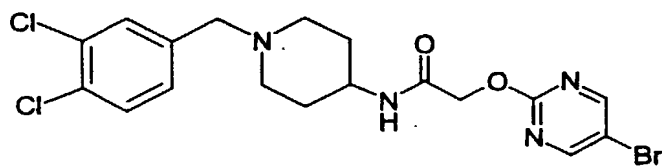


MS  $[\text{M}+\text{H}]^+$  (ES+) 430/32

10  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.40 -1.45 (2H, m), 1.97 (2H, m), 2.15 (2H, m), 2.75 (2H, d), 3.4 (2H, s), 3.8 (1H, m), 4.05 (2H, d), 5.75 (1H, d), 5.84 (1H, m), 6.38 (1H, d), 7.1-7.15 (1H, d), 7.36-7.42(2H, m), 8.0 (1H, d).

**Example 401**

15 **2-[(5-Bromo-2-pyrimidinyl)oxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-acetamide**



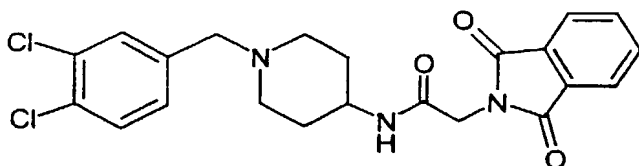
MS  $[\text{M}+\text{H}]^+$  (ES+) 475

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.46-1.50 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.75 (2H, m), 3.4 (2H, s), 3.9 (1H, m), 4.8 (2H, s), 6.38 (1H, d), 7.1-7.15 (1H, m), 7.4 (2H, m), 8.6 (2H, s).

20

**Example 402**

**N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide**

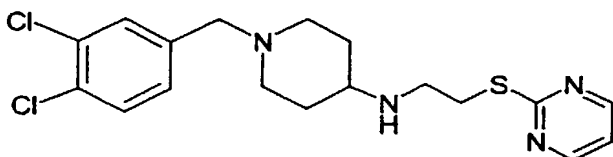


MS  $[M+H]^+$  (ES+) 446

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.46-1.50 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.75 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 4.3 (2H, s), 5.65 (1H, m), 7.1-7.36 (3H, m) 7.38-7.78 (2H, m), 7.87-7.95 (2H, m).

**Example 403**

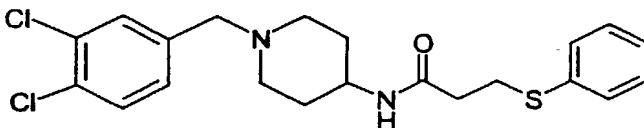
**N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[2-(2-pyridinylthio)ethyl]amine, dihydrochloride**



$^1\text{H NMR}$ : ( $\text{CDCl}_3$ ) (of the free base):  $\delta$  1.4 (2H, m) 1.85 (2H, m), 2.05 (2H, m) 2.55 (2H, td), 2.8 (2H, m), 3.0 (1H, m), 3.3 (2H, m), 3.42 (2H, s), 6.9-7.5 (4H, m), 8.5 (2H, m).

**Example 404**

**N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(phenylthio)propanamide**

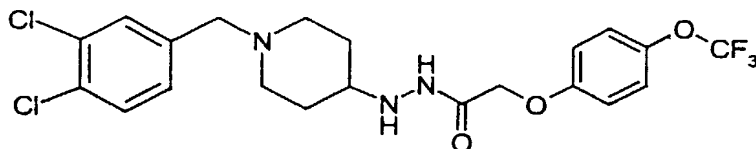


MS  $[M+H]^+$  (ES+) 423

$^1\text{H NMR}$ : ( $\text{CDCl}_3$ )  $\delta$  1.36-1.40 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.45 (2H, m), 2.76 (2H, m), 3.2 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 5.4 (1H, d), 7.1-7.5 (8H, m).

**Example 405**

**N'-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[4-(trifluoromethoxy)phenoxy]acetohydrazide**



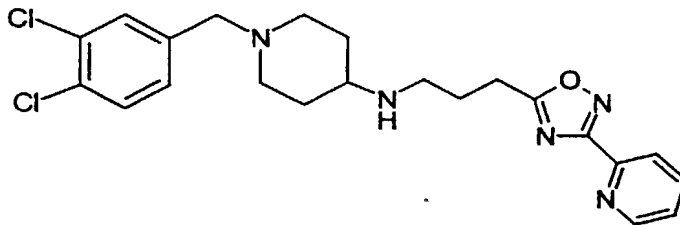
The title compound was prepared from 3,4-dichlorobenzyl-4-piperidone (J. Med. Chem, 1999, 42, 3629; 100mg), 2-[4(trifluoromethoxy)phenoxy]aceto-hydrazide (100mg), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hours in dichloromethane by the method of Example 369 step ii.

MS [M+H]<sup>+</sup> (ES+) 492

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.4–1.6 (3H, m) 1.7 (2H, m), 2.0 (2H, m) 2.7–2.9 (2H, m), 3.4 (2H, m), 4.4 (3H, m), 5.3 (1H, s) 6.9 (2H, m), 7.2–7.5 (4H, m), 7.8 (1H, d).

10 **Example 406**

**N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propyl]amine**



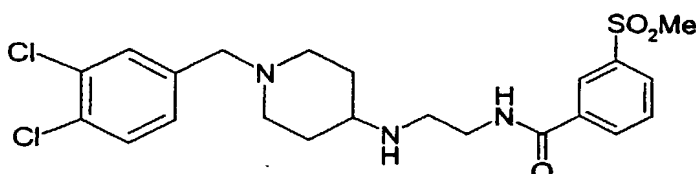
The title compound (29mg) was prepared from 3,4-dichlorobenzylpiperidine-4-amine (100mg free base), 2-[5-(3-bromopropyl)-1,2,4-oxadiazol-3-yl]pyridine (100mg), potassium carbonate (100mg) in dimethyl formamide (1ml) were heated together in the microwave for 30secs, water was added and the product extracted into dichloromethane and chromatographed on silica with ethyl acetate/methanol(9:1) as eluant.

MS [M+H]<sup>+</sup> (ES+) 446

20 <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.4 (2H, m) 1.7–1.9 (4H, m), 2.0–2.1 (4H, m) 2.46 (1H, m), 2.75 (2H, m), 3.1 (2H, t), 3.4 (2H, s), 7.15–7.45 (4H, m), 7.85(1H, t) 8.1 (1H, d) 8.8 (1H, d).

**Example 407**

**N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-(methylsulphonyl)benzamide**



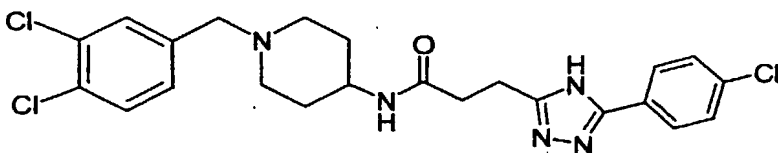
Prepared from *N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2,2,2-trifluoroacetamide (100mg), 3-methylsulphonylbenzoic acid (50mg) and carbonyldiimidazole (40mg). The product obtained was stirred together with sodium hydroxide (40mg) in 50:50 methanol/ water for 12hrs, extracted into dichloromethane and purified by chromatography on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (25mg).

MS [M+H]<sup>+</sup> (ES+) 485

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.4 (2H, m) 1.9 (2H, m), 2.0-2.1 (1H, m) 2.6 (1H, m), 2.8 (2H, m), 2.95 (2H, m) 3.1 (3H, m) 3.4 (2H, s), 3.6 (2H, m), 7.15 (2H, m), 7.4 (2H, m), 7.65(1H, t) 8.1 (2H d) 8.4 (1H, d).

**Example 408**

**3-[5-(4-chlorophenyl)-4H-1,2,4-triazol-3-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide**

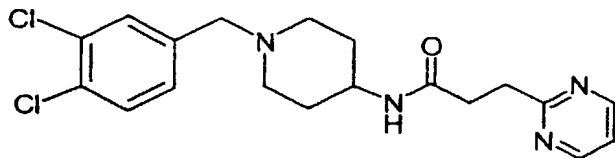


MS [M+H]<sup>+</sup> (ES+) 493

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.6 (2H, m), 1.87 (2H, m), 2.25 (2H m), 2.65 (2H, m), 2.86 (2H, m), 3.14 (2H, m), 3.5 (2H, s), 3.85 (1H, m), 6.0 (1H, m) 7.23 (1H, m), 7.4 (3H m), 7.45 (1H m), 8.0 (2H m).

**Example 409**

**N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(2-pyridinyl)propanamide**

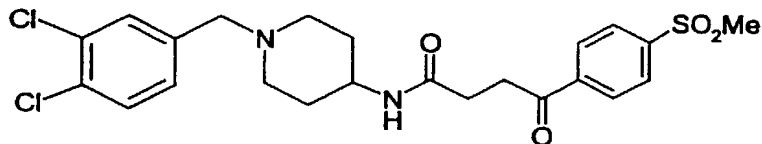


MS [M+H]<sup>+</sup> (ES+) 394

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.46 (2H, m), 1.8 (2H, m), 2.15 (2H, m), 2.75 (4H, m), 3.3 (2H, m), 3.45 (2H, s), 3.8 (1H, m), 6.05 (1H, m), 7.1 (2H, m), 7.38 (1H, m), 7.45 (1H, m), 8.65 (2H, m)

**Example 410**

**N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-4-(4-(methylsulphonyl)phenyl)-4-oxobutanamide**

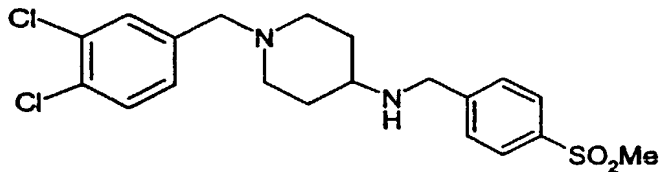


MS [M+H]<sup>+</sup> (ES+) 497

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.4-1.5 (2H, m), 1.9 (2H, m), 2.15 (2H, m), 2.65 (2H, m), 2.78 (2H, m), 3.1 (3H, s), 3.35 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 5.55 (1H, m), 7.16 (1H, m), 7.38 (2H, m), 8.05 (2H, m), 8.2 (2H, m).

**Example 411**

**N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-N'-[4-(methylsulphonyl) benzylamine]**



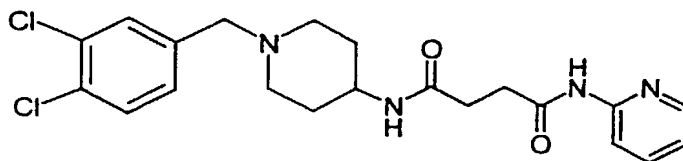
MS [M+H]<sup>+</sup> (ES+) 427

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.4 (2H, m), 1.8-1.9 (2H, m), 2.0 (2H, m), 2.5 (2H, td), 2.8 (2H, m), 3.0 (2H, s), 3.4 (2H, s), 3.94 (2H, s), 7.15 (1H, m), 7.4 (2H, m), 7.55 (2H, d), 7.9 (2H, d).



**Example 412**

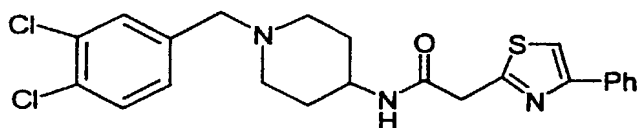
N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-N'-[(2-pyridinyl) succinamide

MS [M+H]<sup>+</sup> (ES+) 435

5 <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.6 (2H, m), 1.87 (2H, m), 2.05 (2H, m), 2.65 (2H, m), 2.76 (4H, m), 3.4 (2H, s), 3.8 (1H, m), 5.65 (1H, m), 7.0 (1H, m), 7.1 (1H, m), 7.38 (2H, d), 7.7 (1H, m), 8.2 (1H, m), 8.27 (1H, m), 8.65 (1H, m).

**Example 413**

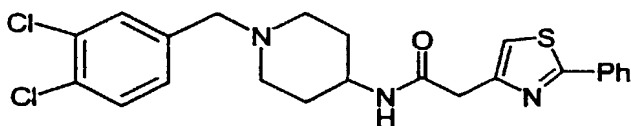
10 N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-(4-phenyl-1,3-thiazol-2-yl)acetamide

MS [M+H]<sup>+</sup> (ES+) 461

15 <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.50 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.65 (2H, m), 3.4 (2H, s), 3.85 (1H, m), 4.0 (2H, s), 7.15 (1H, d) 7.3-7.5 (6H, m), 7.9 (2H, d).

**Example 414**

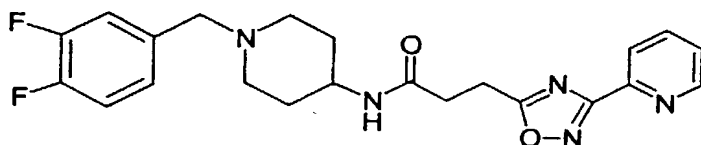
N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-(2-phenyl-1,3-thiazol-4-yl)acetamide

MS [M+H]<sup>+</sup> (ES+) 461

20 <sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 1.45 (2H, m), 1.90 (2H, m), 2.15 (2H, m), 2.65 (2H, m), 3.25 (2H, s), 3.7 (2H, s), 3.85 (1H, m), 7.15 (2H, m) 7.4 (2H, d), 7.5 (3H, m), 8.0 (2H, m).

**Example 415**

**N-[1-(3,4-difluorobenzyl)-4-piperidiny]-3-(3-2-pyridinyl-1,2,4-oxadiazol-5-yl)propanamide**

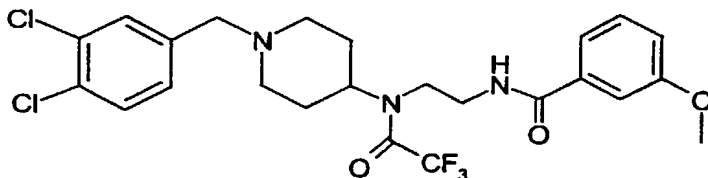


MS [M+H]<sup>+</sup> (ES+) 428

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.36-1.45 (2H, m), 2.0 (2H, m), 2.1-2.2 (2H, t), 2.7-2.85 (4H, m), 3.34 (2H, d), 3.4(2H, d), 3.8 (1H, m), 5.6 (1H, d), 7.0-7.2 (3H m), 7.4 (1H m), 7.8 (1H, m) 8.1 (1H, d), 8.8 (1H, d)

**Example 416**

**N-trifluoroacetyl-N-[2-[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]ethyl]-3-methoxybenzamide**



**a) *tert*-butyl 2-([1-(3,4-dichlorobenzyl)-4-piperidiny]amino)ethylcarbamate**

The sub-titled compound (800mg) was prepared from 3,4-dichlorobenzyl-4-piperidone (1.3g) *tert*-butyl 2-aminoethylcarbamate (0.8g), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane. The sub-titled compound was isolated by standard procedures.

MS [M+H]<sup>+</sup> (ES+) 402

**b) *N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2,2,2-trifluoroacetamide**

A mixture of the above amine (800mg), and triethylamine (0.5ml) in dichloromethane (50ml), treated with trifluoroacetic anhydride (420mg) over 30 mins, evaporated to dryness and dichloromethane(20ml) and trifluoroacetic acid (2ml) added, stirred for 3hrs, then neutralised with aqueous sodium bicarbonate, the organic phase separated, dried and evaporated to give the title compound (250mg) as a yellow oil.

MS [M+H]<sup>+</sup> (ES+) 496/8

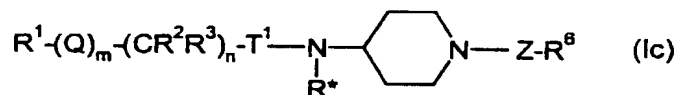
c) **N-trifluoroacetyl-N-[2-[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]ethyl]-3-methoxybenzamide**

The title compound (30mg) was prepared from the product above (40mg) 3-methoxybenzoyl chloride (20mg) and triethylamine (50mg) using one of the methods described above.

MS  $[M+H]^+$  (ES+) 580

$^1H$  NMR: (CDCl<sub>3</sub>)  $\delta$  0.9 (6H, m), 1.2-1.4 (6H, m), 1.6-1.85 (4H, m), 2.8 (1H, m), 3.3 (4H, m), 3.6-3.8 (5H, m), 3.8 (2H, s), 7.0 (1H, m), 7.1 (1H, m), 7.35-7.45 (3H, m), 8.25 (1H, t).

Further compounds of formula (I), all according to formula (Ic), are shown in the table below.



| Example | R <sup>1</sup>                            | (Q) <sub>m</sub> | (CR <sup>2</sup> R <sup>3</sup> ) <sub>n</sub> | T <sup>1</sup> | R <sup>*</sup>  | Z                               | R <sup>6</sup>  |
|---------|---|------------------|--|----------------|-----------------|---------------------------------|---|
| 380     | 4-Cl-C <sub>6</sub> H <sub>4</sub>        | O                | CH <sub>2</sub>                                | C(O)           | H               | CH <sub>2</sub> C<br>(O)NH      | 2-Cl-5-<br>CH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> |
| 381     | 4-Cl-C <sub>6</sub> H <sub>4</sub>        | O                | CH <sub>2</sub>                                | C(O)           | H               | (CH <sub>2</sub> ) <sub>3</sub> | C <sub>6</sub> H <sub>5</sub>                             |
| 382     | 3-(pyridin-2-yl)-<br>1,2,4-oxadiazol-5-yl | O                | CH <sub>2</sub>                                | C(O)           | H               | allyl                           | C <sub>6</sub> H <sub>5</sub>                             |
| 383     | 2-(cyclopropyl-NH)-<br>pyrimidin-4-yl     | m=0              | n=0  | -              | CH <sub>3</sub> | CH <sub>2</sub>                 | 3,4-Cl <sub>2</sub> -<br>C <sub>6</sub> H <sub>3</sub>    |
| 384     | 2-(pyridin-3-yl)-<br>pyrimidin-4-yl       | m=0              | n=0  | -              | CH <sub>3</sub> | CH <sub>2</sub>                 | 3,4-Cl <sub>2</sub> -<br>C <sub>6</sub> H <sub>3</sub>    |
| 400     | pyrimidin-2-yl                            | S                | CH <sub>2</sub>                                | C(O)           | H               | C(O)                            | 3,4-Cl <sub>2</sub> -<br>C <sub>6</sub> H <sub>3</sub>    |

**Pharmacological Analysis**

15 **Calcium flux [Ca<sup>2+</sup>]<sub>i</sub> assay**

**a) Human eosinophils**

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells

were resuspended ( $5 \times 10^6 \text{ ml}^{-1}$ ) and loaded with  $5 \mu\text{M}$  FLUO-3/AM + Pluronic F127  $2.2 \mu\text{l/ml}$  (Molecular Probes) in low potassium solution (LKS; NaCl 118mM,  $\text{MgSO}_4$  0.8mM, glucose 5.5mM,  $\text{Na}_2\text{CO}_3$  8.5mM, KCl 5mM, HEPES 20mM,  $\text{CaCl}_2$  1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at  $2.5 \times 10^6 \text{ ml}^{-1}$ . The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with  $5 \mu\text{M}$  fibronectin for two hours) at 100ml/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200 $\mu\text{l}$ ; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an  $A_{50}$  concentration of eotaxin and the transient increase in fluo-3 fluorescence ( $I_{\text{Ex}} = 490\text{nm}$  and  $I_{\text{Em}} = 520\text{nm}$ ) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

#### 15 b) Human monocytes

Human monocytes were isolated from EDTA anticoagulated peripheral blood as previously described (Cunoosamy & Holbrook, J. Leukocyte Biology, 1998, S2, 13). Cells were resuspended ( $5 \times 10^6 \text{ ml}^{-1}$ ) in LKS and loaded with  $5 \mu\text{M}$  FLUO-3/AM + Pluronic F127  $2.2 \mu\text{l/ml}$  (Molecular Probes) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at  $0.5 \times 10^6 \text{ ml}^{-1}$ . The cells were then transferred to 96 well FLIPr plates (Costar). To each well 100 $\mu\text{l}$  of cells were added at a concentration of  $0.5 \times 10^6 \text{ ml}^{-1}$ . The plates were centrifuged (200g; 5 mins; room temperature) to allow the cells to adhere. After centrifugation the cells were washed twice with LKS (200 $\mu\text{l}$ ; room temperature).

25 A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an  $A_{50}$  concentration of MIP-1 $\alpha$  and the transient increase in fluo-3 fluorescence ( $I_{\text{Ex}} = 490\text{nm}$  and  $I_{\text{Em}} = 520\text{nm}$ ) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of the Examples were found to be antagonists of the eotaxin mediated  $[Ca^{2+}]_i$  in human eosinophils and/or antagonists of the MIP-1 $\alpha$  mediated  $[Ca^{2+}]_i$  in human monocytes.

#### 5 **Human eosinophil chemotaxis**

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at  $10 \times 10^6 \text{ ml}^{-1}$  in RPMI containing 200 IU/ml penicillin, 200  $\mu\text{g/ml}$  streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

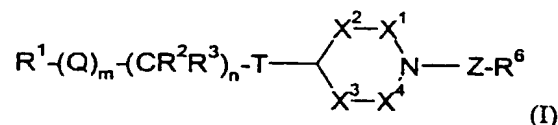
10 Eosinophils (700  $\mu\text{l}$ ) were pre-incubated for 15 mins at 37° C with 7  $\mu\text{l}$  of either vehicle or compound (100x required final concentration in 10% dimethylsulphoxide). The chemotaxis plate (ChemoTx, 3 $\mu\text{m}$  pore, Neuroprobe) was loaded by adding 28 $\mu\text{l}$  of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter  
15 was then placed over the wells and 25  $\mu\text{l}$  of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO<sub>2</sub> atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline  
20 (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28  $\mu\text{l}$  of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to  
25 the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

## CLAIMS

1. The present invention provides a compound of formula (I):



5 wherein

Z is  $CR^4R^5$ , C(O) or  $CR^4R^5-Z^1$ ;

$Z^1$  is  $C_{1-4}$  alkylene,  $C_{2-4}$  alkenylene or C(O)NH;

$R^1$  represents a  $C_1$ - $C_{12}$  alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio,  $C_{3-7}$  cycloalkyl,  $C_1$ - $C_6$  alkoxy carbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, phenyl( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $S(O)_2$ ( $C_1$ - $C_6$  alkyl), C(O)NH<sub>2</sub>, carboxy or  $C_1$ - $C_6$  alkoxy carbonyl); or  $R^1$  represents  $C_2$ - $C_6$  alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, phenyl( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $S(O)_2$ ( $C_1$ - $C_6$  alkyl), C(O)NH<sub>2</sub>, carboxy or  $C_1$ - $C_6$  alkoxy carbonyl); or

$R^1$  represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_6$  hydroxyalkyl,  $C_1$ - $C_6$  haloalkyl,  $C_{1-6}$  alkoxy( $C_1$ - $C_6$  alkyl),  $C_{3-7}$  cycloalkyl( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkylthio( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkylcarbonyloxy( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkyl $S(O)_2$ ( $C_1$ - $C_6$  alkyl), aryl( $C_1$ - $C_6$  alkyl), heterocyclyl( $C_1$ - $C_6$  alkyl), aryl $S(O)_2$ ( $C_1$ - $C_6$  alkyl), heterocyclyl $S(O)_2$ ( $C_1$ - $C_6$  alkyl), aryl( $C_1$ - $C_6$  alkyl) $S(O)_2$ , heterocyclyl( $C_1$ - $C_6$  alkyl) $S(O)_2$ ,  $C_2$ - $C_6$  alkenyl,  $C_1$ - $C_6$  alkoxy, carboxy-substituted  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $C_1$ - $C_6$  hydroxyalkoxy,  $C_1$ - $C_6$  alkylcarboxy-substituted  $C_1$ - $C_6$  alkoxy, aryloxy, heterocyclioxy,  $C_1$ - $C_6$  alkylthio,  $C_{3-7}$  cycloalkyl( $C_1$ - $C_6$  alkylthio),  $C_3$ - $C_6$  alkynylthio,  $C_1$ - $C_6$  alkylcarbonylamino,  $C_1$ - $C_6$  haloalkylcarbonylamino,  $SO_3H$ ,  $-NR^7R^8$ ,  $-C(O)NR^{23}R^{24}$ ,  $S(O)_2NR^{18}R^{19}$ ,  $S(O)_2R^{20}$ ,  $R^{25}C(O)$ , carboxyl,  $C_1$ - $C_6$  alkoxy carbonyl, aryl and heterocyclyl;

wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl;

5 m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR<sup>9</sup>, C(O), C(O)NR<sup>9</sup>, NR<sup>9</sup>C(O) or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R<sup>2</sup> and R<sup>3</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group, or

10 (CR<sup>2</sup>R<sup>3</sup>)<sub>n</sub> represents C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub> alkyl;

T represents a group NR<sup>10</sup>, C(O)NR<sup>10</sup>, NR<sup>11</sup>C(O)NR<sup>10</sup> or C(O)NR<sup>10</sup>NR<sup>11</sup>;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are, independently, CH<sub>2</sub>, CHR<sup>12</sup> {wherein each R<sup>12</sup> is, independently, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)} or C=O; or, when they are CHR<sup>12</sup>, the R<sup>12</sup> groups of X<sup>1</sup> and X<sup>3</sup> or X<sup>4</sup>, or, X<sup>2</sup> and X<sup>3</sup> or X<sup>4</sup> join to form a two or three atom chain

15 which is CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>OCH<sub>2</sub> or CH<sub>2</sub>SCH<sub>2</sub>; provided always that at least two of X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are CH<sub>2</sub>;

R<sup>4</sup> and R<sup>5</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

R<sup>6</sup> is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylcarbonyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl),

20 heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl), arylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarboxy-substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heterocycliloxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkylthio), C<sub>3</sub>-C<sub>6</sub> alkynylthio, C<sub>1</sub>-C<sub>6</sub> alkylcarbonylamino, C<sub>1</sub>-C<sub>6</sub> haloalkylcarbonylamino, SO<sub>3</sub>H, -NR<sup>16</sup>R<sup>17</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, S(O)<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, S(O)<sub>2</sub>R<sup>15</sup>,

25 R<sup>26</sup>C(O), carboxyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl;

30

$R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}$  and  $R^{24}$  are, independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl); and,

$R^{15}$  and  $R^{20}$  are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by phenyl;

$R^{25}$  and  $R^{26}$  are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is C(O)NR<sup>10</sup> and R<sup>1</sup> is optionally substituted phenyl then n is not 0.

2. A compound according to claim 1, wherein Q represents a sulphur atom or a group NH, C(O) or NHC(O).

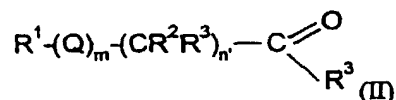
3. A compound according to claim 1 or claim 2, wherein T represents a group NH, C(O)NH or NHC(O)NH.

4. A compound according to any one of claims 1 to 3, wherein X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are all CH<sub>2</sub>.

5. A compound as defined in any one of Examples 1 to 416.

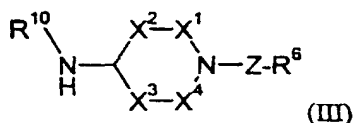
6. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

(a) when n is at least 1, the CR<sup>2</sup>R<sup>3</sup> group attached directly to T is CHR<sup>3</sup> and T is NR<sup>10</sup>, reacting a compound of general formula



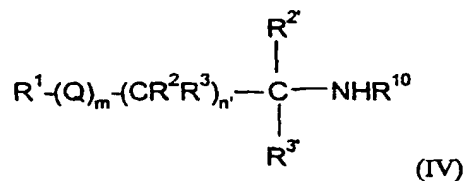


wherein  $n'$  is 0 or an integer from 1 to 3 and  $R^1, R^2, R^3, m$  and  $Q$  are as defined in formula (I), with a compound of general formula

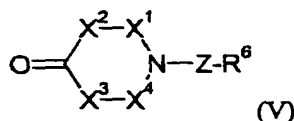


or a salt thereof, wherein  $X^1, X^2, X^3, X^4, Z, R^6$  and  $R^{10}$  are as defined in formula (I), in the presence of a reducing agent; or

(b) when  $n$  is at least 1, the  $CR^2R^3$  group attached directly to  $T$  is  $C(C_1-C_4 \text{ alkyl})_2$  and  $T$  is  $NR^{10}$ , reacting a compound of general formula

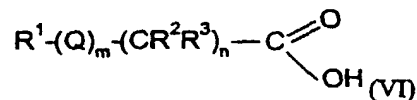


wherein  $n'$  is 0 or an integer from 1 to 3,  $R^2$  and  $R^3$  each independently represent a  $C_1-C_4$  alkyl group, and  $R^1, R^2, R^3, R^{10}, m$  and  $Q$  are as defined in formula (I), with a compound of general formula



wherein  $X^1, X^2, X^3, X^4, Z$  and  $R^6$  are as defined in formula (I), in the presence of a reducing agent; or

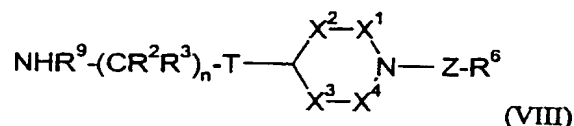
(c) when  $T$  is  $C(O)NR^{10}$ , reacting a compound of general formula



wherein  $R^1, R^2, R^3, Q, m$  and  $n$  are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

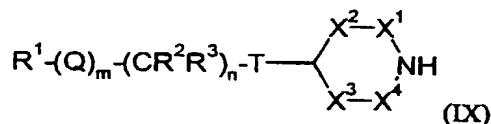
(d) when  $m$  is 1 and  $Q$  is  $\text{NR}^9$ , reacting a compound of general formula (VII),  $\text{R}^1 - \text{L}^1$ , wherein  $\text{L}^1$  represents a leaving group (e.g. a halogen atom) and  $\text{R}^1$  is as defined in formula (I), with a compound of general formula

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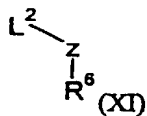
or a salt thereof, wherein  $n$ ,  $\text{T}$ ,  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$ ,  $\text{X}^4$ ,  $\text{Z}$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^6$  and  $\text{R}^9$  are as defined in formula (I); or

10 (e) when at least one of  $\text{R}^4$  and  $\text{R}^5$  represents a hydrogen atom, reacting a compound of general formula



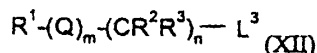
15 or a salt thereof, wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{Q}$ ,  $m$ ,  $n$ ,  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$ ,  $\text{X}^4$  and  $\text{T}$  are as defined in formula (I), with a compound of general formula (X),  $\text{R}^6 - \text{C}(\text{O}) - \text{R}^{20}$ , wherein  $\text{R}^{20}$  represents a hydrogen atom or a  $\text{C}_1$ - $\text{C}_4$  alkyl group and  $\text{R}^6$  is as defined in formula (I), in the presence of a reducing agent; or

20 (f) reacting a compound of formula (IX) as defined in (e) above, with a compound of general formula



wherein  $\text{L}^2$  represents a leaving group (e.g. a halogen atom) and  $\text{Z}$  and  $\text{R}^6$  are as defined in formula (I); or

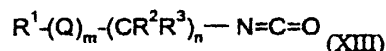
25 (g) when  $\text{T}$  is  $\text{NR}^{10}$ , reacting a compound of general formula



wherein  $L^3$  represents a leaving group (e.g. a halogen atom) and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $m$ ,  $n$  and  $Q$  are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

5

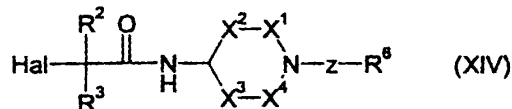
(h) when  $T$  is  $\text{NHC(O)NR}^{10}$ , reacting a compound of general formula



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $Q$ ,  $m$  and  $n$  are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

10

(i) when  $T$  is  $\text{C(O)NH}$ ,  $Z$  is  $\text{CH}_2$ ,  $n$  is 1,  $R^2$  and  $R^3$  are hydrogen or  $\text{C}_1$ - $\text{C}_4$  alkyl and  $Q$  is oxygen or sulphur, reacting a compound of formula (XIV):



wherein  $\text{Hal}$  is a suitable halogen,  $R^2$ ,  $R^3$ ,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $Z$  and  $R^6$  are as defined in formula (I), with  $\text{R}^1\text{OH}$  or  $\text{R}^1\text{SH}$  in the presence of a suitable base;

15

and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

20

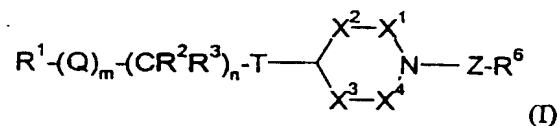
7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25

8. A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 for use in therapy.

5 10. Use of a compound of formula (I),



wherein

Z is  $CR^4R^5$ , C(O) or  $CR^4R^5-Z^1$ ;

$Z^1$  is  $C_{1-4}$  alkylene,  $C_{2-4}$  alkenylene or C(O)NH;

- 10  $R^1$  represents a  $C_1$ - $C_{12}$  alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio,  $C_3$ - $C_7$  cycloalkyl,  $C_1$ - $C_6$  alkoxycarbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, phenyl( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $S(O)_2$ ( $C_1$ - $C_6$  alkyl), C(O)NH<sub>2</sub>, carboxy or  $C_1$ - $C_6$  alkoxycarbonyl); or
- 15  $R^1$  represents  $C_2$ - $C_6$  alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, phenyl( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $S(O)_2$ ( $C_1$ - $C_6$  alkyl), C(O)NH<sub>2</sub>, carboxy or  $C_1$ - $C_6$  alkoxycarbonyl); or
- $R^1$  represents a 3- to 14-membered saturated or unsaturated ring system which optionally
- 20 comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_6$  hydroxyalkyl,  $C_1$ - $C_6$  haloalkyl,  $C_{1-6}$  alkoxy( $C_1$ - $C_6$  alkyl),  $C_3$ - $C_7$  cycloalkyl( $C_1$ - $C_6$  alkyl),
- 25  $C_1$ - $C_6$  alkylthio( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkylcarbonyloxy( $C_1$ - $C_6$  alkyl),  $C_1$ - $C_6$  alkylS(O)<sub>2</sub>( $C_1$ - $C_6$  alkyl), aryl( $C_1$ - $C_6$  alkyl), heterocyclyl( $C_1$ - $C_6$  alkyl), arylS(O)<sub>2</sub>( $C_1$ - $C_6$  alkyl), heterocyclylS(O)<sub>2</sub>( $C_1$ - $C_6$  alkyl), aryl( $C_1$ - $C_6$  alkyl)S(O)<sub>2</sub>, heterocyclyl( $C_1$ - $C_6$  alkyl)S(O)<sub>2</sub>,  $C_2$ - $C_6$  alkenyl,  $C_1$ - $C_6$  alkoxy, carboxy-substituted  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $C_1$ - $C_6$  hydroxyalkoxy,  $C_1$ - $C_6$  alkylcarboxy-substituted  $C_1$ - $C_6$  alkoxy, aryloxy, heterocyclyloxy,
- 30  $C_1$ - $C_6$  alkylthio,  $C_3$ - $C_7$  cycloalkyl( $C_1$ - $C_6$  alkylthio),  $C_3$ - $C_6$  alkynylthio,  $C_1$ - $C_6$

alkylcarbonylamino, C<sub>1</sub>-C<sub>6</sub> haloalkylcarbonylamino, SO<sub>3</sub>H, -NR<sup>7</sup>R<sup>8</sup>, -C(O)NR<sup>23</sup>R<sup>24</sup>,  
 S(O)<sub>2</sub>NR<sup>18</sup>R<sup>19</sup>, S(O)<sub>2</sub>R<sup>20</sup>, R<sup>25</sup>C(O), carboxyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, aryl and heterocyclyl;  
 wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or  
 more of halogen, oxo, hydroxy, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub>  
 5 alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub>  
 alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR<sup>9</sup>, C(O), C(O)NR<sup>9</sup>, NR<sup>9</sup>C(O) or  
 CH=CH;

10 n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R<sup>2</sup> and R<sup>3</sup> independently represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group, or  
 (CR<sup>2</sup>R<sup>3</sup>)<sub>n</sub> represents C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub> alkyl;

T represents a group NR<sup>10</sup>, C(O)NR<sup>10</sup>, NR<sup>11</sup>C(O)NR<sup>10</sup> or C(O)NR<sup>10</sup>NR<sup>11</sup>;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are, independently, CH<sub>2</sub>, CHR<sup>12</sup> {wherein each R<sup>12</sup> is, independently,  
 15 C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl)} or C=O; or, when they are CHR<sup>12</sup>, the R<sup>12</sup>  
 groups of X<sup>1</sup> and X<sup>3</sup> or X<sup>4</sup>, or, X<sup>2</sup> and X<sup>3</sup> or X<sup>4</sup> join to form a two or three atom chain  
 which is CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>OCH<sub>2</sub> or CH<sub>2</sub>SCH<sub>2</sub>; provided always that at least two  
 of X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> are CH<sub>2</sub>;

R<sup>4</sup> and R<sup>5</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

20 R<sup>6</sup> is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano,  
 nitro, oxo, hydroxyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub>  
 alkyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub>  
 alkylcarbonyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-C<sub>6</sub> alkyl),

heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl), arylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), heterocyclylS(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), aryl(C<sub>1</sub>-  
 25 C<sub>6</sub> alkyl)S(O)<sub>2</sub>, heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy-  
 substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarboxy-  
 substituted C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heterocyclioxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-  
 C<sub>6</sub> alkylthio), C<sub>3</sub>-C<sub>6</sub> alkynylthio, C<sub>1</sub>-C<sub>6</sub> alkylcarbonylamino, C<sub>1</sub>-C<sub>6</sub>

haloalkylcarbonylamino, SO<sub>3</sub>H, -NR<sup>16</sup>R<sup>17</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, S(O)<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, S(O)<sub>2</sub>R<sup>15</sup>,

30 R<sup>26</sup>C(O), carboxyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing  
 aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro,

cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl;

R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup> and R<sup>24</sup> are, independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl); and,

R<sup>15</sup> and R<sup>20</sup> are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl) or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by phenyl;

R<sup>25</sup> and R<sup>26</sup> are, independently, C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub>

10 alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), C(O)NH<sub>2</sub>, carboxy or C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, in the manufacture of a medicament for the modulation of a chemokine receptor.

- 15 11. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, as defined claim 10.

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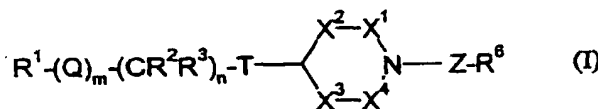
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(54) Title: SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



and conditions.

(57) Abstract: The invention provides compounds of formula (I) wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, Z, Q, m, n, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup> and T are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them, and their use in therapy, especially for the treatment of chemokine receptor related diseases

10/069215

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PATENT

ATTORNEY DOCKET NO: 06275/244US1

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY, the specification of which

- is attached hereto.
was filed on as Application Serial No. and was amended on
x was described and claimed in PCT International Application No. PCT/GB00/03179 filed on 18 August 2000 and as amended under PCT Article 19 on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Table with 4 columns: COUNTRY, APPLICATION NO., FILING DATE, PRIORITY CLAIMED. Row 1: SE, 9902987-8, 24 August 1999, x Yes [ ] No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Table with 3 columns: U.S. SERIAL NO, FILING DATE, STATUS. Row 1: [ ], [ ], [ ] Pending [ ] Issued [ ] Abandoned

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

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